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OFFICE OF
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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

February 24, 2011

SUBJECT: **Difenoconazole** Human Health Risk Assessment for Amended Section 3 Registration to Add Uses on Carrots, Chickpeas, Soybeans, Stone Fruits (Group 12), Strawberries, Turnip Greens and Golf Course Turf Grass

PC Code: 128847
Decision No.: 426124

Petition No.: PP#9F7676
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: 386946
Registration No.: 100-1262, 100-1312, 100-1313, 100-1317
Regulatory Action: Section 3 New Use
Case No.: 7014
CAS No.: 119446-68-3
40 CFR: §180.475

FROM: Becky Daiss, Biologist Becky Daiss
Bonnie Cropp-Kolligian, Environmental Scientist
Thurston Morton, Chemist
Risk Assessment Branch 4
Health Effects Division (7509P)

THROUGH: Deborah Smegal, Acting Branch Chief
Susan V. Hummel, Branch Senior Scientist
Risk Assessment Branch 4
Health Effects Division (7509P)

Deborah C Smegal
Susan V Hummel

TO: Rosemary Kearns/Tony Kish (RM 22)
Fungicide Branch
Registration Division (7505P)

This document provides the Health Effects Division's (HED's) risk assessment of requested new use of difenoconazole on carrots, chickpeas, soybeans, stone fruits, strawberries, turnip greens and turf grass on golf courses. This document also updates previous residential and occupational exposure assessments on existing uses to incorporate a new dermal absorption factor and updated occupational and residential exposure scenarios.

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1.0 EXECUTIVE SUMMARY

This assessment provides information to support an amended Section 3 registration for the use of difenoconazole in/on carrots, chickpeas, soybeans, stone fruits (group 12), strawberries, turnip greens and golf course turf and establishment of associated tolerances. This document assesses risks associated with exposures resulting from currently registered and proposed new use of difenoconazole. It also assesses potential enhanced sensitivity of infants and children from dietary and/or residential exposure as required under the Food Quality Protection Act (FQPA) of 1996.

Use Profile

Difenoconazole is a broad spectrum fungicide belonging to the triazole group of fungicides. It is currently registered in the U.S. for use as a seed treatment on cereal grains, canola, and cotton and for foliar applications to numerous food crops and ornamentals. Tolerances for difenoconazole, currently established under 40 CFR §180.475, range from 0.01-35 ppm. Difenoconazole acts by blocking demethylation during sterol biosysnthesis which, in turn, disrupts membrane synthesis. Difenoconazole is available as liquid emulsifiable concentrate, soluble concentrate, and ready-to-use formulations. As a seed treatment, it is applied with commercial grade seed treatment equipment. Difenoconazole is applied to field and vegetable crops and landscape ornamentals by commercial applicators using aerial and ground application methods and equipment. It is applied to ornamentals by residential applicators using hand held sprayers.

Proposed New Uses

Syngenta Crop Protection Inc., is requesting an amended registration for a 1.05 lb ai/gal soluble concentrate (SC) formulation of difenoconazole and azoxystrobin Quadris Top® Fungicide (EPA Reg No 100-1313) to add a golf course turf use and an alternative brand name, Heritage Top® for the golf course use product. The proposed maximum application rate is 0.25 lbs active ingredient (ai) per acre with a reapplication interval of 14-21 days and a maximum seasonal use rate of 0.52 lbs ai per acre per year.

Syngenta is also requesting an amended registration for a 2.08 lb/gal emulsifiable concentrate (EC) formulation (Inspire™ Fungicide; 100-1262) to add uses on carrots, chickpeas, soybeans, stone fruits, and strawberries. In addition, Syngenta is proposing to add some or all of these proposed food uses to the following multiple active ingredient products: a 2.08 lb/gal MAI EC formulation with propiconazole (Inspire™ XT Fungicide; EPA Reg. No. 100-1312); a 1.05 lb/gal MAI suspension concentrate (SC) formulation with azoxystrobin (Quadris Top™ Fungicide; EPA Reg. No. 100-1313); and a 0.73 lb/gal MAI emulsion oil in water (EW) formulation with cyprodinil (Inspire Super ™ Fungicide; EPA Reg. No. 100-1317). The EC product formulations (EPA Reg. Nos. 100-1262 and 100-1312) are proposed for multiple foliar applications at 0.09-0.114 lb ai/A/application for maximum seasonal rates of 0.46 lb ai/A on carrots, chickpeas (EPA Reg. No. 100-1262 but not EPA Reg. No. 100-1312), soybeans, stone fruits, and strawberries. The proposed minimum preharvest intervals (PHIs) are 7 days for

carrots (14 days for EPA Reg. No. 100-1312), 14 days for chickpeas and soybeans, and 0 days for stone fruits and strawberries. The SC formulation product (EPA Reg. No. 100-1313) and the EW formulation product (EPA Reg. No. 100-1317) are proposed for the same crops, except that the EW formulation is not proposed for use on soybeans, with essentially the same use patterns and the same minimum PHIs. There is a proposed restriction against the feeding of soybean hay, forage and silage which is considered to be under grower control.

Hazard Identification

Subchronic and chronic studies with difenoconazole in mice and rats showed decreased body weights, decreased body weight gains and effects on the liver. Acute and subchronic neurotoxicity studies showed evidence of neurotoxic effects. However, the observed effects were transient and dose-response was well characterized with identified no observed adverse effect levels (NOAELs). There are no indications of immunotoxicity in the available studies. Chronic effects in rats and mice are seen as cumulative decreases in body weight gains. No evidence of carcinogenicity was seen in rats. Evidence for carcinogenicity was seen in mice as induction of liver tumors at doses which were considered to be excessively high for carcinogenicity testing. Treatment-related non-neoplastic lesions were confined to the liver. Difenoconazole has been classified as "Suggestive Evidence of Carcinogenic Potential" with risk quantitated using a non-linear (Margin of Exposure) approach. The cancer classification is based on excessive toxicity observed at the two highest doses, the absence of tumors at the lower doses and the absence of genotoxic effects. The FQPA Safety Factor is reduced to 1X. Difenoconazole exhibits low acute toxicity by the oral, dermal and inhalation routes of exposure. It is not an eye or skin irritant and is not a sensitizer.

The toxicological database for difenoconazole is sufficient to conduct this risk assessment. However, in accordance with Part 158 Toxicology Data requirements, an immunotoxicity study (870.7800) is required for difenoconazole.

Dose Response Assessment

Toxicological points of departure (PODs) were selected for dietary/drinking water, occupational, and non-occupational exposure scenarios based on registered and proposed new uses of difenoconazole. Acute and chronic PODs were selected for assessment of food and drinking water exposures. An acute POD for all populations was selected from an acute neurotoxicity study in rats based on reduced grip strength. A chronic POD was selected from a chronic/carcinogenicity study in rats based on body weight effects. Short and intermediate-term incidental oral, dermal and inhalation PODs were selected from an oral rat reproduction study based on decreased body weight effects in pups and parental animals. A dermal absorption factor is applied when dermal exposure endpoints are selected from oral toxicity studies. The dermal factor converts the oral dose to an equivalent dermal dose for the risk assessment. A dermal absorption factor of 6% was used for the dermal exposure assessment. This factor was derived based on data from a triple pack of a 28 rat *in vivo* dermal absorption study and *in vitro* dermal absorption studies conducted with rat and human skin. Inhalation toxicity is assumed to

be equivalent to oral toxicity. An uncertainty factor of 100X was applied endpoints selected for all exposures routes (10X for interspecies extrapolation, 10X for intraspecies variation).

Exposure/Risk Assessment and Risk Characterization

Risk assessments were conducted for dietary (food and water), occupational and non-occupational (residential) exposure pathways based on registered uses and proposed new uses of difenoconazole on food commodities and golf course turf. Occupational and residential exposure assessments of previously registered uses have been revised to incorporate new dermal absorption data and updated exposure scenarios. Screening level acute and refined chronic dietary and drinking water risk assessments indicate that for all commodities, dietary and drinking water exposure estimates are below HED's level of concern. Risk estimates for worker and residential handler and post-application exposure scenarios exposures are not of concern at maximum use rates for existing and proposed new uses. Aggregate risks are not of concern.

Use of Human Studies

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, listed in Appendix B have been determined to require a review of their ethical conduct. Some of these studies are also subject to review by the Human Studies Review Board. All of the studies used have received the appropriate review.

2.0 HED RECOMMENDATIONS

Data Deficiencies

Based on HED's examination of the residue chemistry database for difenoconazole, pending submission of a revised Section B (Directions for Use) and a revised Section F (Proposed Tolerances), there are no residue chemistry issues that would preclude granting a conditional registration for the requested uses of the EC, SC, and EW formulations of difenoconazole on carrots, chickpeas, soybeans, stone fruits (group 12), strawberries, turnip greens. The following additional data are required to satisfy the conditions of registration: (1) additional storage stability data for the triazole metabolites in crop matrices, processed commodities, and livestock commodities; (2) additional confined rotational crop data reflecting phenyl-ring labeling which were previously required under PP#6F7115 (D344680, 11/5/07, M. Sahafeyan); (3) additional soybean field trials conducted with the SC formulation at the maximum proposed use rate, and (4) additional EC and EW bridging data. Storage stability data for the triazole metabolites in various crop matrices, processed commodities and livestock have been requested as part of the Human Health Aggregate Risk Assessment for the triazole metabolites (M. Doherty, D322215, 2/7/06). The required storage stability data on crop matrices and processed commodities have been submitted and are being reviewed. These data are expected to satisfy crop and processed commodity storage stability data requirements for the proposed new uses. The required storage stability data for triazole residues in livestock, when

submitted, are expected to satisfy livestock storage stability data requirements for the proposed new uses. A confined rotational crop study has been submitted and is under review. An immunotoxicity study (870.7800) is required for difenoconazole.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

An adequate enforcement method, GC/NPD method AG-575B, is available for the determination of residues of difenoconazole *per se* in/on plant commodities. An adequate enforcement method, LC/MS/MS method REM 147.07b, is available for the determination of residues of difenoconazole and CGA-205375 in livestock commodities. Adequate confirmatory methods are also available.

2.2.2 International Harmonization

Codex maximum residue levels (MRLs) for residues of difenoconazole *per se* have been established at 0.2 ppm for carrot; 0.02 ppm for soya bean (dry); 0.2 ppm for cherries and plums (including prunes); and 0.5 ppm for nectarines and peaches. Canadian and Mexican MRLs have been established for difenoconazole; however, no MRLs have been established for the commodities included in the current petition. Codex MRLs for residues of difenoconazole and its metabolite CGA-205375, expressed as difenoconazole have been established at 0.2 ppm for edible offal (mammalian) and 0.01 for eggs. Also, Canadian MRLs have been established for difenoconazole at 0.05 ppm for meat byproducts of cattle, goats, hogs, and sheep and at 0.05 ppm in eggs. Based on the submitted/available magnitude of the residue data, harmonization with established Codex MRLs is not possible for carrots, soya bean (dry), cherries, plums (including prunes), nectarines, peaches, edible offal (mammalian), and eggs because the Codex MRLs are too low. Harmonization with the established Canadian MRLs for eggs and meat byproducts of cattle, goats, hogs, and sheep is not possible due to differences in the regulated residue expression. Also based on the available magnitude of the residue data, harmonization with established Canadian MRLs is not possible for meat byproducts of cattle, goats, hops, and sheep because the Canadian MRLs are too low.

2.2.3 Recommended Tolerances

Based on HED's examination of the residue chemistry database for difenoconazole, pending submission of a revised Section B (see requirements under Section 2.2.5) and a revised Section F (see requirements under Section 2.2.4), there are no residue chemistry issues that would preclude granting a conditional registration for the requested uses of the EC, SC, and EW formulations of difenoconazole or establishment of tolerances for residues of difenoconazole in/on the following commodities:

Aspirated grain fractions.....95 ppm
Carrot .....0.50 ppm

Chickpea	0.08 ppm
Fruit, stone, group 12	2.5 ppm
Soybean, hulls	0.20 ppm
Soybean, seed	0.15 ppm
Strawberry	2.5 ppm
Turnip greens	35 ppm

HED recommends increasing the permanent tolerances for residues of difenoconazole and its metabolite, CGA-205375 [1-[2-chloro-4-(4-chloro-phenoxy)phenyl]-2-[1,2,4]triazol-1-yl-ethanol] in liver of cattle, goat, hog, horse, and sheep from 0.20 ppm to 0.40 ppm.

Cattle, liver	0.40 ppm
Goat, liver	0.40 ppm
Hog, liver	0.40 ppm
Horse, liver	0.40 ppm
Sheep, liver	0.40 ppm

HED recommends lowering the permanent tolerance for residues of difenoconazole and its metabolite, CGA-205375 [1-[2-chloro-4-(4-chloro-phenoxy)phenyl]-2-[1,2,4]triazol-1-yl-ethanol] in egg from 0.10 ppm to 0.02 ppm.

Egg	0.2 ppm

2.2.4 Revisions to Petitioned-For Tolerances

HED's recommended revisions to the tolerances and/or commodity definitions submitted by Syngenta for this new use petition are listed in Table 1. The current tolerance expression for difenoconazole residues of concern in/on raw agricultural commodities listed under 40 CFR §180.475(a)(1) is consistent with HED's Interim Guidance on Tolerance Expressions (5/27/09, S. Knizner); however, the current tolerance expression for difenoconazole residues of concern in livestock commodities listed under 40 CFR §180.475(a)(2) should be revised to state: "Tolerances are established for residues of difenoconazole, including its metabolites and degradates, in the commodities in the following table. Compliance with the tolerance levels specified below is to be determined by measuring the sum of difenoconazole, 1-[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole, and its metabolite, CGA-205375, 1-[2-chloro-4-(4-chloro-phenoxy)phenyl]-2-[1,2,4]triazol-1-yl-ethanol, calculated as the stoichiometric equivalent of difenoconazole, in the following commodities:" Section F of the subject petition should be revised as needed to reflect the correct tolerance expression, tolerance level, and commodity definition.

Table 1. Summary of Revisions to Petitioned for Tolerances for Difenoconazole			
Commodity	**Proposed Tolerance (ppm)**	**Recommended Tolerance (ppm)**	***Correct Commodity Definition;* Comments**
Carrot	0.45	0.50	
Chickpeas	0.05	0.08	*Chickpea*
Soybean, seed	0.20	0.15	
Soybean, hulls	None	0.20	
Soybean, aspirated grain fraction	95	95	*Aspirated grain fractions*
Fruits, stone, group 12	2.5	2.5	*Fruit, stone, group 12*
Strawberry	2.5	2.5	
Turnip greens	35	35	
Milk	0.08	0.01	No change to the currently established tolerance (0.01 ppm) is warranted.
Liver of cattle, goat, hog, horse, and sheep	None	0.40	Based on the dietary burden, the currently established tolerance should be increased from 0.20 ppm to 0.40 ppm.
Eggs	None	0.02	*Egg* Currently established tolerance should be decreased from 0.10 ppm to 0.02 ppm.

2.2.5 Label Recommendations

The proposed 7-day minimum retreatment interval for chickpeas is not supported by the residue data. Labels for chickpea uses must be revised to specify a minimum retreatment interval of 14 days for chickpeas. The proposed 0.46 lb ai/A maximum seasonal application rate for soybeans is not supported by the residue data. Labels for soybean use must be revised to specify a maximum seasonal application rate of 0.22 lb ai/A. Turnip greens should be added to the list of Brassica leafy vegetables specified on the following labels, Inspire™ Fungicide (EPA Reg. No. 100-1262), Quadris Top™ Fungicide (EPA Reg. No. 100-1313) and Inspire Super™ Fungicide (EPA Reg. No. 100-1317). Okra must be removed from the list of crops on the Quadris Top™ Fungicide Label (EPA Reg. No. 100-1313) permitting a 0-day plantback interval (PBI). For strawberries, the use rate on the label for Quadris Top™ Fungicide (EPA Reg. No. 100-1313 and should be 8-14 fl. oz. product/A.

3.0 INGREDIENT PROFILE

3.1 Registered Products

There are 28 active difenoconazole registrations, 16 Section 3 uses and 12 Section 18 Emergency Exemptions.

Table 2. Summary Report of Supported Registered Difenoconazole-P Products [S-difenoconazole]			
Reg #	**Name**	**Company Name**	**%AI**
100-739	Difenoconazole Technical	Syngenta Crop Protection, Inc.	95
100-740	Dividend Fungicide	Syngenta Crop Protection, Inc.	32.8
100-826	Dividend Xl Rta	Syngenta Crop Protection, Inc.	3.21
100-885	Dividend Xl	Syngenta Crop Protection, Inc.	16.5
100-935	Helix Xtra Insecticide With Fungicides	Syngenta Crop Protection, Inc.	1.25
100-973	Helix Insecticide With Fungicides	Syngenta Crop Protection, Inc.	1.24
100-1141	Dividend Extreme Fungicide	Syngenta Crop Protection, Inc.	7.73
100-1255	Difeno-Shield	Syngenta Crop Protection, Inc.	32.8
100-1262	Inspire	Syngenta Crop Protection, Inc.	23.2
100-1278	Revus Top	Syngenta Crop Protection, Inc.	21.9
100-1286	Quartet Cotton Seed Treatment Fungicide	Syngenta Crop Protection, Inc.	0.35
100-1305	Cruiser Maxx Cereals	Syngenta Crop Protection, Inc.	3.36
100-1312	Inspire Xt	Syngenta Crop Protection, Inc.	22.8
100-1313	Quadris Top	Syngenta Crop Protection, Inc.	11.4
100-1317	Inspire Super	Syngenta Crop Protection, Inc.	8.4
100-1335	Difenoconazole/Mefenoxam Fs	Syngenta Crop Protection, Inc.	3.37

3.2 Pesticide Use Pattern

Difenoconazole is currently registered in the U.S. for use as a seed treatment on cereal grains, canola, and cotton and for foliar applications to numerous fruit and vegetable crops and ornamentals. Proposed new uses include difenoconazole use on carrots, chickpeas, soybeans, stone fruits, strawberries, turnip greens and turfgrass on golf courses. Maximum application rates for existing and proposed new uses on food commodities and turf are provided in Table 3. Maximum rates are based on a review of active labels.

Table 3. Maximum Application Rates for Difenoconazole Existing and Proposed Uses					
Application Site	**% AI**	**Max Single App Rate**	**Max Seasonal App Rate**	**Application Method**	**Reg No.**
Existing Use – Citrus[1]	23.2	0.125 lb ai/A	0.5 lb ai/A	aerial, ground, chemigation	100-1262 EC[2]
Existing Use – Ornamentals		0.13 lb ai/A	0.56 lb ai/A	aerial, ground, chemigation	
Existing Use – Seed Treatment	32.8	0.0305 lb ai/100 lb seed	0.0305 lb ai/100 lb seed	commercial treatment	100-740 SC[3]
Proposed New Use – Golf Course Turf	11.4	0.25 lb ai/A	0.52 lb ai/A	ground	100-1313 SC
Proposed New Use – Strawberry, Carrot, Chickpeas, Soybean, Stone Fruit	23.2	0.114 lb ai/A	0.46 lb ai/A	aerial, ground, chemigation	100-1262 EC

[1]Maximum application rates are lower for all other registered tree fruit uses (i.e., 0.114 lb ai/A)
[2] EC – Emulsifiable Concentrate
[3] SC – Soluble Concentrate

3.3 Structure, Nomenclature, and Physical/Chemical Properties

Nomenclature and physicochemical properties of difenoconazole are provided in Tables 4 and 5.

Table 4. Difenoconazole Nomenclature.

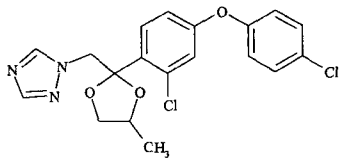
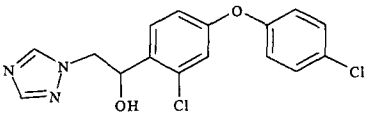
Chemical structure	
Common name	Difenoconazole
Company experimental name	CGA-169374
IUPAC name	1-({2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl}methyl)-1H-1,2,4-triazole
CAS name	1-[[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole
CAS registry number	119446-68-3
End-use products (EP)	Inspire™, 2.08 lb/gal EC (EPA Reg. No. 100-1262); Inspire™ XT Fungicide, 2.08 lb/gal MAI EC formulation with propiconazole (EPA Reg. No. 100-1312); Quadris Top™ Fungicide, 1.05 lb/gal MAI SC formulation with azoxystrobin (EPA Reg. No. 100-1313); and Inspire Super™ Fungicide, 0.73 lb/gal MAI EW formulation with cyprodinil (EPA Reg. No. 100-1317). Quadris Top® Fungicide 1.05 lb ai/gal soluble concentrate (SC) formulation of difenoconazole and azoxystrobin (EPA Reg No 100-1313).
Chemical structure of CGA-205375 livestock metabolite	

Table 5. Physicochemical Properties of Difenoconazole.

Parameter	Value	Reference
Melting point	78.6 °C	DP#s 172067 and 178394, 10/26/92, R. Lascola
pH	6-8 at 20 °C (saturated solution)	
Density	1.37 g/cm^3 at 20 °C	
Water solubility	3.3 ppm at 20 °C	
Solvent solubility	g/100 mL at 25 °C: n-hexane: 0.5 1-octanol: 35 toluene: 77 acetone: 88 ethanol: 89	
Vapor pressure	2.5 x 10^{-10} mm Hg at 25 °C	
Dissociation constant, pK_a	pure grade (99.3% ± 0.3%) difenoconazole in water (with 4% methanol) at 20°C is 1.1	DP# 375159, 5/26/10, B. Cropp-Kohlligian

Table 5. Physicochemical Properties of Difenoconazole.		
Parameter	**Value**	**Reference**
Octanol/water partition coefficient, Log(K_{OW})	4.2 at 25 °C	DP#s 172067 and 178394, 10/26/92, R. Lascola
UV/visible absorption spectrum	λ_{max} at about 200 and 238 nm (in methanol at 26 °C)	PMRA Proposed Regulatory Decision Document on Difenoconazole, 4/14/99 (PRDD99-01)

3.4 Considerations of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post application are evaluated. Further considerations are currently in development, as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 HAZARD CHARACTERIZATION/ASSESSMENT

4.1 Hazard Characterization

The toxicology database for difenoconazole is adequate for evaluating and characterizing difenoconazole toxicity and selecting endpoints for purposes of this risk assessment.

Subchronic and chronic studies with difenoconazole in mice and rats showed decreased body weights, decreased body weight gains and effects on the liver. In an acute neurotoxicity study in rats, reduced fore-limb grip strength was observed on day 1 in males and clinical signs of neurotoxicity were observed in females at the limit dose of 2000 mg/kg. In a subchronic neurotoxicity study in rats, decreased hind limb strength was observed in males only at the mid- and high-doses. However, the effects observed in acute and subchronic neurotoxicity studies are transient, and the dose-response is well characterized with identified NOAELs. No systemic toxicity was observed at the limit dose in the most recently submitted 28-day rat dermal toxicity study.

There is no concern for increased qualitative and/or quantitative susceptibility after exposure to difenoconazole in developmental toxicity studies in rats and rabbits, and a

reproduction study in rats as fetal/offspring effects occurred in the presence of maternal toxicity. There are no indications in the available studies that organs associated with immune function, such as the thymus and spleen, are affected by difenoconazole.

In accordance with HED's current policy and EPA's 2005 Cancer Guidelines, difenoconazole is classified as "Suggestive Evidence of Carcinogenic Potential." In 1994, HED's Cancer Peer Review Committee (CPRC) recommended a cancer classification of C (possible human carcinogen) based on liver tumors observed in mice at 300 ppm and higher, the absence of tumors at two lower doses of 10 and 30 ppm, excessive toxicity observed at the two highest doses of 2500 and 4500 ppm, the absence of genotoxic and no evidence of carcinogenicity in rats. The CPRC also advocated use of an MOE approach to risk assessment using the chronic point of departure (POD) based on effects observed in the chronic mouse study relevant to tumor development (*i.e.*, hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis). In 2007, the CPRC Chair reaffirmed the MOE approach as an appropriate method to address concerns for chronic toxicity and cancer. The POD is considered protective of the cancer effects.

Difenoconazole possesses low acute toxicity by the oral, dermal and inhalation routes of exposure. It is not an eye or skin irritant and is not a sensitizer.

The toxicity profiles for difenoconazole are provided in Appendix A.

4.2 Absorption, Distribution, Metabolism and Excretion

The absorption, distribution, metabolism, and excretion of difenoconazole were studied in rats. The test compound was labeled with C^{14} at either the phenyl or triazole ring. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg of radiolabeled compound or 0.5 mg/kg unlabeled compound by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C]-difenoconazole on day 15. Difenoconazole undergoes successive oxidation and conjugation reactions. [^{14}C]-difenoconazole was rapidly and extensively distributed, metabolized, and excreted in rats for all dosing regimens. The extent of absorption is undetermined because the extent of biliary excretion was not identified. Difenoconazole metabolites accounted for most of the recovered radioactivity in the excreta. The 4-day recoveries were 97.4- 107.75% of the administered dose for all dosing groups. The elimination of radioactivity in the feces (78.06- 94.61% of administered dose) and urine (8.48-21.86%) were almost comparable for all oral dose groups, with slightly higher radioactivity found in the feces of the high dose group than the low dose groups. This was probably due to biliary excretion, poor absorption or saturation of the metabolic pathway. Radioactivity in the blood peaked at about 24-48 hours for all dosing groups. Half-lives of elimination appear to be approximately 20 hours for the low dose groups and 33 - 48 hours for the high dose group. One difenoconazole metabolite, CGA-205375, accounts for 6-24% of the applied dose and is found only in urine and feces of oral high-dose rats. The presence of this intermediate in excreta of only high-dose rats suggests that its rate of further biotransformation has reached saturation at the high dose.

4.3 FQPA Hazard Considerations

The toxicity database is sufficient for a full hazard evaluation and is considered adequate to evaluate risks to infants and children. Acceptable acute and subchronic neurotoxicity studies are available. An immunotoxicity study is required. This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses).

4.3.1 Neurotoxicity

In an acute neurotoxicity study in rats, reduced fore-limb grip strength was observed on day 1 in males and clinical signs of neurotoxicity were observed in females at the limit dose of 2000 mg/kg. The effect in males is considered transient since it was not observed at later observation points. Toxicity in females was observed only at doses exceeding the limit dose. In a subchronic neurotoxicity study in rats decreased hind limb strength was observed in males only. The effects observed in acute and subchronic neurotoxicity studies are transient, and the dose-response is well characterized with identified NOAELs. Based on the toxicity profile, and lack of concern for neurotoxicity, a developmental neurotoxicity study in rats is not required.

4.3.2 Developmental Toxicity

In a rat developmental toxicity study developmental effects were observed at doses higher than those which caused maternal toxicity. Developmental effects in the rat included increased incidence ossification of the thoracic vertebrae and hyoid, decreased number of sternal centers of ossification, increased number of ribs and thoracic vertebrae, and decreased number of lumbar vertebrae. In the rabbit study, developmental effects (increases in post-implantation loss and resorptions and decreases in fetal body weight) were also seen at maternally toxic doses.

4.3.3 Reproductive Toxicity

In a two generation reproduction study in rats, reproductive effects (decreased pup weights) were seen only at doses which also caused maternal parental toxicity.

4.3.4 Determination of Susceptibility

The available Agency Guideline studies indicated no increased susceptibility of rats or rabbits to in utero and/or from postnatal exposure to difenoconazole. In the prenatal developmental toxicity studies in rats and rabbits and the two-generation reproduction study in rats, toxicity to the fetuses/offspring, when observed, occurred at equivalent or higher doses than in the maternal/parental animals.

4.3.5 FQPA Safety Factor Recommendation

The FQPA factor for increased susceptibility to infant and children is reduced to 1x based on the following considerations:

- The toxicology data base for difenoconazole is complete and adequate for assessing increased susceptibility under FQPA.
- There is no indication of increased susceptibility of rats or rabbit fetuses to in utero and/or postnatal exposure in the developmental and reproductive toxicity data.
- There are no residual uncertainties in the exposure database.
- The dietary risk assessment is conservative and will not underestimate dietary exposure to difenoconazole.

4.4 Toxicity Endpoint Selection

4.4.1 Acute Population Adjusted Doses (aPAD) – All Populations

Selected Study: Acute Neurotoxicity Study in Rats (MRID 46950327).

In an acute neurotoxicity study, rats (10/sex/dose) were given a single oral dose of difenoconazole technical (94.3% ai) in 1% w/v aqueous carboxymethylcellulose at doses of 0, 25, 200, or 2000 mg/kg bw and observed for 14 days. At 2000 mg/kg, a number of adverse clinical signs were observed on day 1 (at the time of peak effect), including: upward curvature of the spine; tip-toe gait; decreased activity; piloerection; sides pinched in and subdued. Females were affected more than males. All treatment-related clinical signs observed on day 1 showed complete recovery by day 5 (males) or day 7 (females). Significant decreases in fore-limb grip strength were seen in mid- and high-dose males on day 1. Females dosed with 2000 mg/kg had lower motor activities on day 1 at the time of peak effect, and on day 8. Males dosed with 200 or 2000 mg/kg had higher motor activities than the controls on day 1 at the time of peak effect. The LOAEL is 200 mg/kg bw based on reduced fore-limb grip strength in males on day 1 and increased motor activity on Day 1. The NOAEL is 25 mg/kg bw.

Dose and Endpoint for Establishing an aPAD: NOAEL is 25 mg/kg/day. LOAEL is 200 mg/kg/day based on reduced fore-limb grip strength in males on day 1.

Uncertainty Factor (UF): 100 This includes 10x for interspecies extrapolation and 10x for intraspecies variation.

Comments about Study/Endpoint: The selected endpoint is considered appropriate for acute dietary exposure because effects were seen after a single dose. The endpoint is protective of the general population and all subpopulations for effects seen in the acute neurotoxicity study in rats. It is also protective of developmental and maternal effects observed in the rabbit developmental toxicity study at the LOAEL of 75 mg/kg/day and NOAEL of 25 mg/kg/day.

General Population aPAD = $\frac{\text{(NOAEL) 25 mg/kg}}{\text{(UF) 100}}$ = 0.25 mg/kg

4.4.2 Chronic Population Adjusted Dose (cPAD) – All Populations

Selected Study: Chronic/Oncogenicity Study in Rats (MRID 42090019/20)

In a chronic cancer feeding study, difenoconazole was administered in the diet to male and female rats for 104 weeks at 0; 10; 20; 500; and 2500 ppm. There were reductions in cumulative body weight gains in the 500 and the 2500 ppm groups. Mean liver weight was increased at week 53 and at termination in the 2500 ppm group. Hepatocellular hypertrophy was observed in the 500 and the 2500 ppm animals at termination. The NOAEL for the study is 20 ppm (0.96 and 1.27 mg/kg/d for males and females respectively). The LOAEL is 500 ppm (24.12 and 32.79 mg/kg/day for males and females respectively) based on cumulative decreases in body weight gains.

Dose and Endpoint for Establishing an cPAD: The NOAEL is 0.96 mg/kg/day. The LOAEL is 24.12 mg/kg/day based on cumulative decreases in body weight gains at 24.12 mg/kg/day in males.

Uncertainty Factor (UF): 100 This includes 10X for interspecies extrapolation and 10x for intraspecies variation.

$$\textbf{General Population cPAD} = \frac{\textbf{(NOAEL) 0.96 mg/kg/day}}{\textbf{(UF) 100}} = \textbf{0.01 mg/kg/day}$$

4.4.3 Incidental Oral Exposure (Short-Term)

Selected Study: Two Generation Reproduction Study in Rats (MRID 42090018)

In a two generation reproduction study, difenoconazole was administered in the diet to male and female rats at 0, 25, 250, or 2500 ppm [0; 1.25, 12.5, or 125 mg/kg/day, respectively]. Statistically significant reductions in body weight gains of F0 and F1 males were observed at 2500 ppm during the course of the study. There was a significant reduction in the body weight of F1 male pups on Day 21 in the 250 ppm group. The percentage of male pups in the F1 generation surviving Days 0-4 was significantly reduced in the 2500 ppm group. For parental toxicity, the LOAEL of 250 ppm (12.5 mg/kg/day) is based on the decreased maternal body weight gain; the NOAEL is 25 ppm (1.25 mg/kg/day). For offspring toxicity, the LOAEL of 250 ppm (12.5 mg/kg/day) is based on decreased pup weights at Day 21; the NOAEL is 25 ppm (1.25 mg/kg/day).

Dose and Endpoint for Establishing POD: The NOAEL is 1.25 mg/kg/day based on decreased pup weight in males at 12.5 mg/kg/day (LOAEL) on day 21, and reductions in body weight gain in F0 females.

Uncertainty Factor (UF): An MOE 100 is required for the short- and intermediate-term scenarios for dermal exposure is based on the conventional uncertainty factor of 100. This

includes 10x for interspecies extrapolation and 10x for intraspecies variation.

Comments about Study/Endpoint: There are no residential uses for difenoconazole that would result in incidental oral exposure to children. However, a short term oral exposure endpoint is required for aggregate risk assessment.

4.4.4 Dermal Absorption

A dermal absorption factor (DAF) is applied when dermal exposure endpoints are selected from oral toxicity studies. The dermal factor converts the oral dose to an equivalent dermal dose for the risk assessment. A DAF of 6% was selected for use in risk assessment based on available in vivo dermal absorption studies in rat and in vitro dermal absorption studies conducted with rat and human skin. The DAF was selected by a special working group of the Antimicrobials Division Toxicity Endpoint Selection Committee (12/18/08 memorandum from J. Chen to M. Swindell – Attachment A.3).

4.4.5 Dermal Exposure (Short and Intermediate-Term)

Selected Study: Two Generation Reproduction Study in Rats (MRID 42090018)

See Section 4.4.3

Dose and Endpoint for Establishing POD: The NOAEL is 1.25 mg/kg/day based on decreased pup weight in males at 12.5 mg/kg/day (LOAEL) on day 21 and reductions in body weight gain in F0 females.. Dermal absorption is 6%.

Uncertainty Factor (UF): An MOE 100 is required for the short- and intermediate-term scenarios for dermal exposure is based on the conventional uncertainty factor of 100. This includes 10x for interspecies extrapolation and 10x for intraspecies variation.

Comments about Study/Endpoint: Although dermal toxicity studies are available, a POD from an oral study was selected because effects in young animals (decreased pup weight) the primary effect of concern for short, intermediate and long term exposure is not specifically evaluated in the available dermal toxicity studies that only assess adult animals. The selected endpoint is protective of offspring effects from dermal exposure. A DAF of 6% is applied to the POD for dermal exposure.

4.4.6 Inhalation Exposure (Short- and Intermediate-Term)

Selected Study: Two Generation Reproduction Study in Rats (MRID 42090018)

See Section 4.4.3

Dose and Endpoint for Establishing POD: The NOAEL is 1.25 mg/kg/day based on decreased pup weight in males at 12.5 mg/kg/day (LOAEL) on day 21 and reductions in body

weight gain in F0 females.

Uncertainty Factor (UF): An MOE 100 is required for the short- and intermediate-term scenarios for inhalation exposure is based on the conventional uncertainty factor of 100. This includes 10x for interspecies extrapolation and 10x for intraspecies variation.

Comments about Study/Endpoint: A route specific study is not available. The POD selected from the oral study is protective of reproductive toxicity, the primary effect of concern for short, intermediate and long term exposure. Inhalation toxicity is assumed to be equivalent to oral toxicity

4.4.7 Classification of Carcinogenic Potential

Difenoconazole is not mutagenic, and no evidence of carcinogenicity was seen in rats. Evidence for carcinogenicity was seen in mice, where liver tumors were induced at doses which were considered to be excessively high for carcinogenicity testing. Liver tumors were observed in mice at 300 ppm and higher; however, based on excessive toxicity observed at the two highest doses of 2500 and 4500 ppm (females terminated after two weeks due to excessive toxicity resulting in moribundity and death), the absence of tumors at two lower doses of 10 and 30 ppm and the absence of genotoxic effects. In accordance with HED's current policy and EPA's 2005 Cancer Guidelines, difenoconazole is classified as "Suggestive Evidence of Carcinogenic Potential," based on excessive toxicity observed at the two highest doses, the absence of tumors at the lower doses and the absence of genotoxic effects. A margin-of-exposure (MOE) approach in risk assessment was advocated by HED's CPRC in 1994. Use of an MOE approach was reviewed and reaffirmed in 2007 by the CPRC Chair (PV Shah, 3/1/07, HED Doc. No. 0054532). Based on the CPRC recommendation, the risk assessment uses an (MOE) approach utilizing the no-observable-adverse-effects-level (NOAEL) of 30 ppm (4.7 and 5.6 mg/kg/day in males and females, respectively) and the lowest-observable-adverse-effects-level (LOAEL) of 300 ppm (46 and 58 mg/kg/day in males and females, respectively) from the mouse study using only those biological endpoints which were relevant to tumor development (*i.e.*, hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis)

4.4.8 Margins of Exposure

A summary of target Levels of Concern for risk assessment is provided in Table 6.

Table 6. Target Levels of Concern/Margin of Exposure for Difenoconazole

Route/Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	N/A
Inhalation	100	100	N/A
Residential (Non-Dietary) Exposure			
Oral	N/A	N/A	N/A
Dermal	100	N/A	N/A
Inhalation	100	N/A	N/A

NA = not applicable

4.4.9 Recommendation for Aggregate Exposure Risk Assessments

When there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. Oral, dermal and inhalation exposures to residents should be aggregated for difenoconazole because the endpoints selected for these exposure routes are based on common toxicological effects.

4.4.10 Summary of Endpoints Selected for Risk Assessment

Toxicological doses/endpoints selected for the difenoconazole risk assessment are provided in Tables 7 and 8.

Table 7. Summary of Toxicological Doses and Endpoints for Difenoconazole for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, LOC for Risk Assessment	Study and Relevant Toxicological Effects
Acute Dietary (All populations)	NOAEL = 25 mg/kg	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	aRfD = aPAD = 0.25 mg/kg/day	Acute Neurotoxicity Study in Rats LOAEL= 200 mg/kg in males based on reduced fore-limb grip strength in males on day 1.
Chronic Dietary (All populations)	NOAEL = 0.96 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	cRfD = cPAD = 0.01mg/kg/day	Combined chronic toxicity/carcinogenicity (rat; dietary) LOAEL = 24.1/32.8 mg/kg/day (M/F) based on cumulative decreases in body-weight gains.
Incidental Oral Short-Term (1-30 days)	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Residential LOC for MOE<100	Reproduction and fertility Study (rat; dietary) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Dermal Short- and Intermediate- Term (1-30 days and 1-6 months) DAF = 6%	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Residential LOC for MOE<100	Reproduction and fertility Study (rat; dietary) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Inhalation (Short- and Intermediate-term) Inhalation and oral absorption assumed equivalent	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Residential LOC for MOE<100	Reproduction and fertility Study (rat; dietary) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Cancer (oral, dermal, inhalation)	Difenoconazole is classified "Suggestive Evidence of Carcinogenic Potential" with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94, Memo, P. V. Shah dated March 3,			

Table 7. Summary of Toxicological Doses and Endpoints for Difenoconazole for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	RfD, PAD, LOC for Risk Assessment	**Study and Relevant Toxicological Effects**
	2007, HED Doc. No. 0054532).			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data DAF = Dermal Absorption Factor

Table 8. Summary of Toxicological Doses and Endpoints for Difenoconazole for Use Occupational Human Health Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- and Intermediate- Term (1-30 days and 1-6 months) DAF = 6%	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X	Occupational LOC for MOE<100	Reproduction and fertility Study (rat; dietary) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Inhalation (Short- and Intermediate-term) Inhalation and oral absorption assumed equivalent	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X	Occupational LOC for MOE<100	Reproduction and fertility Study (rat; dietary) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Cancer (oral, dermal, inhalation)	Difenoconazole is classified "Suggestive Evidence of Carcinogenic Potential" with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94, Memo, P. V. Shah dated March 3, 2007, HED Doc. No. 0054532).			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key date (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

4.5 Endocrine Disruption

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal

systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain post-application agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors.

Difenoconazole is not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Under FFDCA sec. 408(p) the Agency must screen all pesticide chemicals. Accordingly, EPA anticipates issuing future EDSP test orders/data call-ins for all pesticide active ingredients.

For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

5.0 DIETARY AND DRINKING WATER EXPOSURE AND RISK ASSESSMENT

5.1 Metabolite/Degradate Residue Profile

5.1.1 Metabolism in Primary Crops and Livestock

The nature of the residue in plants is understood based on acceptable plant metabolism studies reflecting foliar applications in canola, grape, potato, tomato, and wheat and seed treatment in wheat. Based on the results of available plant metabolism studies, the petitioner has proposed that difenoconazole is metabolized in plants by the hydroxylation of the phenyl ring and/or cleavage of the dioxolane ring followed by cleavage of the carbon-carbon bridge between the phenyl and triazole rings. The nature of the residue in livestock is understood based on acceptable goat and hen metabolism studies.

5.1.2 Metabolism in Rotational Crops

The available confined rotational crop data are not adequate to support the proposed uses on carrots, chickpeas, soybeans, stone fruits, and strawberries. A confined rotational crop study reflecting phenyl-ring labeling is required at 1x the proposed maximum seasonal foliar application rate (0.46 lb ai/A). Syngenta Crop Protection, Inc. has submitted a confined rotational crop study (MRID 48203402) which is currently under review in HED (D382946).

5.1.3 Comparison of Metabolic Pathways

Little information is available on the toxicity of the major difenoconazole metabolites. The hydroxy difenoconazole metabolite (CGA-205375) formed in livestock appears to be formed in the rat also, and is, therefore, part of the total toxic exposure for these animals. It is unlikely to be more toxic than the parent. The desphenyl metabolite is also unlikely to be more toxic than the parent. It is difficult to know, however, what effect the removal of the entire benzene ring will have on the toxicology. This metabolite is not formed in rats and, therefore, is not a part of the toxic profile to which the rat is exposed when dosed with the parent. After correction for molecular weight differences, the LD_{50} of the parent and of the desphenyl metabolite are similar.

5.1.4 Magnitude of the Residue in Crops

Adequate field trial data have been submitted to support the proposed uses of the EC, SC and EW formulations of difenoconazole on carrots, chickpeas, soybeans, stone fruits, and strawberries provided that the petitioner submits a revised Section B/proposed labels specifying a minimum retreatment interval (RTI) of 14-days for chickpeas and a maximum seasonal use rate of 0.22 lb ai/A for soybeans, and confirmatory field trial data on soybeans. The number and geographic distribution of the field trials are adequate, the appropriate samples were collected at the proposed PHIs, and, with the exceptions note above, the trials were conducted at the maximum proposed labeled use rates. Samples were analyzed for the residues of concern using adequate methods. Required additional soybean field trials conducted with the SC formulation at the maximum proposed use rate may be conducted with a 25% reduction in number or in the form of limited side-by-side trials conducted to compare residues resulting from the use of an EC formulation with use of the SC formulation. For difenoconazole, storage stability data for crop and processed commodities are adequate to support the submitted magnitude of the residue data. For the triazole residues, storage stability data for crop and processed commodities have been submitted and are expected to satisfy data requirements for the proposed new uses. The recommended tolerance for residues of difenoconazole in/on carrots, chickpeas, soybeans, stone fruits (group 12), strawberries, and turnip greens are based primarily on maximum residue levels found in field trials. A summary of recommended tolerances and maximum residues from submitted field trial data is provided in table 9.

Table 9. Difenoconazole: Summary of Recommended Tolerances and Maximum Field Trial Residues for Proposed New Uses

Crop	Recommended Tolerance (ppm)	Maximum Residue (ppm)
Carrot	0.50	0.203
Chickpeas	0.08	0.032
Soybean seed	0.15	0.152 [1]
Stone fruits	2.5	1.02 [2]
Strawberry	2.5	1.22
Turnip greens	35	NA [3]

[1] Highest Average Field Trial = 0.0869

[2] Based on peach data

[3] No turnip green data were provided. Mustard green data were translated to support the recommended tolerance.

5.1.5 Magnitude of the Residue in Livestock and Poultry

Tolerances are currently established for residues of difenoconazole and its metabolite CGA 205375 in livestock and poultry commodities. Based on calculated dietary burdens and the feeding study data for livestock, the established tolerances for milk, meat, fat, and meat byproducts (except liver) are adequate to support the proposed uses; however, the tolerance levels for residues in liver of cattle, goat, hog, horse, and sheep should be increased from 0.20 ppm to 0.40 ppm. The calculated dietary burden and the feeding study data for poultry indicate that no tolerances are needed for these commodities; however, the tolerance level for residues of concern in eggs should be decreased from 0.10 ppm to 0.02 ppm based on the current livestock tolerance enforcement method. Storage stability data for triazole residues in livestock have been requested and are expected to satisfy livestock storage stability data requirements for the proposed new uses, once submitted.

5.1.6 Residue in Processed Commodities

Submitted processing studies conducted with difenoconazole on plum and soybean commodities are considered adequate to fulfill data requirements. The plum processing data indicate that residues of difenoconazole and TA do concentrate in prunes (average processing factors 2.6x and 2.5x, respectively), but residues of 1,2,4-T and TAA do not. Based on the plum processing study data, a separate tolerance is not needed for residues of difenoconazole in prunes. The soybean processing data indicate that residues of difenoconazole do concentrate in hulls and aspirated grain fractions (AGF) (average processing factors 2.0x and 622x, respectively), but not in meal and refined oil. Also residues of TAA concentrate slightly in meal (average processing factor 1.3x) and residues of 1,2,4-T and TAA concentrate in AGF (average processing factors 2.4x and 6.4x, respectively). Based on the recommended tolerance in/on soybean seed (0.15 ppm) and the average processing factor for AGF (622x), a separate tolerance is needed for residues of difenoconazole in/on AGF at 95 ppm.

5.1.7 Residues of Concern Summary and Rationale

Residues of concern were determined based on recommendations from the HED Metabolism Assessment Review Committee (MARC). The residue of concern for plant commodities for tolerance expression and risk assessment purposes is difenoconazole *per se*. The residues of concern in livestock for tolerance setting and risk assessment are difenoconazole and its metabolite CGA 205375. Table 10 summarizes tolerance expression and the residues of concern in plant and livestock commodities.

Table 10. Difenoconazole Residues of Concern in Plants and Ruminants.

Matrix		Residues of Concern	
		For Risk Assessment	For Tolerance Expression
Plants	Primary and Rotational crops	Parent Only	Parent Only
Livestock	Ruminant and Poultry	Parent and CGA 205375	Parent and CGA 205375
Drinking Water		Parent Only	NA

5.2 Estimated Drinking Water Concentrations

The drinking water estimates used in the dietary risk assessment were provided by the Environmental Fate and Effects Division. EFED conducted a drinking water assessment for surface water sources using the Pesticide Root Zone/Exposure Analysis Modeling System (PRZM/EXAMS) for the registered and proposed new uses. Groundwater sources were assessed using the Screening Concentration in Groundwater (SCI-GROW v2.3, Jul. 29, 2003). Among the registered and proposed new uses, the highest estimated drinking water concentrations (EDWCs) for surface water sources were derived for aerial applications of difenoconazole to New York grapes at the maximum annual application rate of 0.46 lb ai/acre. The estimated drinking water residues for 1-in-10 year annual peak, 1-in-10 year annual mean, and 36-year annual mean are 15.8, 10.4, and 7.62 µg/L (ppb) respectively. The highest estimated drinking water concentration of difenoconazole from shallow ground water sources is 1.28×10^{-2} µg/L, obtained for the maximum application rate for ornamentals (0.52 lb ai/A). These concentrations can be considered as both the acute and chronic groundwater values. The EDWCs from ground water sources are expected to be the same for the proposed golf course turf uses as estimated for ornamentals.

5.3 Dietary and Drinking Water Exposure and Risk

Screening level acute and refined chronic dietary and drinking water exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model with the Food Commodity Intake Database (DEEM-FCID™). Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic dietary assessments, the risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). The PAD is equivalent to the POD divided by the uncertainty factors. For acute and non-cancer chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD.

5.3.1 Acute Dietary and Drinking Water Analysis

The unrefined acute analysis assumed tolerance-level residues, 100% crop treated (CT), and the available empirical or DEEM™ (ver. 7.81) default processing factors. The resulting acute food exposure estimates were less than HED's level of concern (<100% of the acute population-adjusted dose (aPAD)) at the 95th percentile of the exposure distribution for the general U.S. population (8 % aPAD) and all population sub-groups; the most highly exposed population subgroup was children1-2 years old with 19 % aPAD.

Table 11. Summary of Acute Dietary Exposure and Risk for Difenoconazole at the 95th Percentile.

Population Subgroup	aPAD (mg/kg/day)	Exposure (mg/kg/day)	%aPAD
General U.S. Population		0.020754	8
All Infants (< 1 year old)		0.039801	16
Children 1-2 years old		**0.047902**	**19**

Table 11. Summary of Acute Dietary Exposure and Risk for Difenoconazole at the 95th Percentile.			
Population Subgroup	**aPAD (mg/kg/day)**	**Exposure (mg/kg/day)**	**%aPAD**
Children 3-5 years old	0.25	0.037248	15
Children 6-12 years old		0.021824	9
Youth 13-19 years old		0.011365	5
Adults 20-49 years old		0.014883	6
Adults 50+ years old		0.019450	8
Females 13-49 years old		0.015260	6

5.3.2 Chronic Dietary and Drinking Water Analysis

The somewhat refined chronic analysis assumed tolerance-level residues for some commodities, average field trial residues for the majority of commodities, the available empirical or DEEM™ (ver. 7.81) default processing factors, and 100 % CT. The resulting chronic food exposure estimates were less than HED's level of concern (<100% of the chronic PAD) for the general U.S. population (18 % cPAD) and all population sub-groups; the most highly exposed population subgroup was children 1-2 years old with 49 % cPAD.

Table 12. Summary of Chronic Dietary Exposure and Risk for Difenoconazole.			
Population Subgroup	**cPAD (mg/kg/day)**	**Exposure (mg/kg/day)**	**%cPAD**
General U.S. Population	0.01	0.001831	18
All Infants (< 1 year old)		0.003058	31
Children 1-2 years old		**0.004889**	**49**
Children 3-5 years old		0.003931	39
Children 6-12 years old		0.002257	23
Youth 13-19 years old		0.001447	15
Adults 20-49 years old		0.001442	14
Adults 50+ years old		0.001659	17
Females 13-49 years old		0.001483	15

The requested uses of difenoconazole resulted in an increase in dietary exposure estimates for free triazole or conjugated triazoles. Therefore, the last dietary exposure analyses for the triazole metabolites has been updated (D386652, T. Morton, 2/16/11).

6.0 RESIDENTIAL EXPOSURE AND RISK

The proposed new label for use of difenoconazole on turf grass limits application of the product to turf grass on golf courses only. Therefore residential applicator exposure is not assessed for the proposed new golf course turf use. Residential post-application exposure to treated golf course turf is possible for recreational golfers, however. Existing uses also include residential application of difenoconazole to ornamentals.

6.1 Residential Handler Exposure

The term "handler" applies to individuals who mix, load, and apply the pesticide product. There is a potential for exposure to difenoconazole during mixing, loading, and application activities through the dermal and inhalation routes. Difenoconazole products are applied by homeowners using handheld spray equipment.

6.1.1 Residential Handler Exposure Scenarios

The following residential handler exposure scenarios evaluated for this assessment are based on information provided in the existing labels.

- Mixing/loading/applying liquid formulation to ornamentals with hose end sprayer
- Mixing/loading/applying liquid formulation to ornamentals with hand held pump sprayer
- Mixing/loading/applying liquid formulation to flower gardens with hose end sprayer
- Mixing/loading/applying mix-your-own liquid formulation to flower gardens with hose end sprayer
- Mixing/loading/applying liquid formulation to flower gardens with hand held pump sprayer

6.1.2 Residential Handler Exposure Data

No chemical-specific handler exposure data were submitted in support of this registration. When chemical-specific monitoring data are not available, it is HEDs policy to use data from the Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments (December 1997), and updates contained in HED's Science Advisory Council Policy 12 (February 2001).

6.1.3 Residential Handler Exposure Assumptions

- Average body weight of an adult handler is 70 kg.
- Dermal Absorption Factor is 6%
- Exposure duration is short-term (1- 30 days) and intermediate-term (1-6 months)
- Maximum label application rate is 0.13 lb ai/A for ornamentals and flower gardens
- Area treated is 0.5 acres per day for handheld sprayer applications to ornamentals and flower gardens
- Clothing – short-sleeved shirt and short pants

6.1.4 Residential Handler Exposure and Risk Estimates

Exposure and risk estimates indicate MOEs are not of concern (MOEs > 100) at the maximum use rate for the residential handler exposure scenarios assessed. A summary of residential applicator exposure and risk calculations, assumptions, and results is provided in Table 13.

Table 13. Estimated Difenoconazole Exposure and MOEs for Residential Handlers Short-Term LOC/MOE = 100										
Exp Scenario	**Inhal Unit Exposure (ug/lb ai)[1]**	**Dermal Unit Exposure (mg/lb ai)[1]**	**Appl Rate (lb ai/A) [2]**	**Area Treated (A/day)[3]**	**Inhal Dose (mg/kg/ day)[4]**	**Inhal MOE**	**Dermal Dose (mg/kg/d) [5]**	**Dermal MOE**	**Agg dose (mg/kg/d)**	**Agg MOE[6]**
Mix/Load/Apply to Ornamentals										
Hose End Sprayer	1.5	39	0.13	0.5	0.0000	897436	0.0022	575	0.0022	575
Hose-end Sprayer Mix Your Own	17	11	0.13	0.5	0.0000	79186	0.0006	2040	0.0006	1988
Handheld Pump Spray	3.8	56	0.13	0.5	0.0000	354251	0.0031	401	0.0031	400
Mix/Load/Apply to Flower Garden										
Hose End Sprayer	0.82	34	0.13	0.5	0.0000	1641651	0.0019	660	0.0019	660
Handheld Pump Spray	2.7	38	0.13	0.5	0.0000	498575	0.0021	590	0.0021	590

[1] Unit exposure values are reported Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments (December 1997), and updates contained in HED's Science Advisory Council Policy 12 (February 2001)
[2] Application rates based on labels .
[3] Amount treated based on information provided ExpoSAC Policy 9
[4] Inhalation dose (mg/kg/event) = [unit exposure (kg/lb ai) * (1mg/1000 kg) conversion * appl. rate (lb ai/lbs seed) * Amount treated / body weight (70 kg)].
[5] Dermal dose (mg/kg/event) = [unit dermal exposure (mg/lb ai) * application rate (lb ai/A) * Amount treated *DAF/ body weight (70 kg)].
[6] Agg MOE = NOAEL (1.25 mg/kg/day)/Dermal + Inhalation Daily Dose. The LOC is 100.

6.2 Residential Post-Application Exposure

HED uses the term "post-application" to describe those individuals who can be exposed to pesticides after entering areas previously treated with pesticides and performing certain tasks or activities (also often referred to as reentry exposure).

6.2.1 Residential Post-Application Exposure Scenarios

Based on the proposed new use on golf course turf, dermal exposures were assessed for adult and child recreational golfer. Ornamental uses are not expected to result in significant post-application exposures. Based on the Agency's current practices, a quantitative post application inhalation exposure assessment was not performed for difenoconazole. However, volatilization of pesticides may be a potential source of post application inhalation exposure to individuals nearby to pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 and is in the process of evaluating the SAP report. The Agency may, as appropriate, develop policies and procedures to identify the need for and, subsequently, the way to incorporate post application inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative post application inhalation exposure assessment.

6.2.2 Residential Post-Application Exposure Data

Maximum application rates for all of the exposure scenarios assessed are based on information provided in the proposed difenoconazole label for application to golf course turf. The residential post-application risk assessment is based on assumptions and methods from SOPs established by HED' Science Advisory Council for Exposure (ExpoSAC).

6.2.3 Residential Post-Application Exposure Assumptions

- Average adult body weight is 70 kg
- Average older child (golfer) body weight is 39 kg
- Dermal absorption factor = 6%
- Exposure is assumed to occur on the day of application (day 0)
- Turf Transferrable residue is 5% of the application rate for the fraction initially available.
- Transfer coefficient is 500 cm^2/hour for golfers
- Exposure duration is 4 hours per day for golfers

6.2.4 Residential Post-Application Exposure and Risk

Exposure and risk estimates indicate MOEs are not of concern (MOEs > 100) at the maximum use rate for the residential post-application exposure scenario assessed. A summary of residential post-application exposure and risk calculations, assumptions, and results is provided in Table 14.

Table 14. Estimated Difenoconazole Exposure & MOEs for Post-application Dermal Exposure to Treated Lawn/Golf Course Turf LOC/MOE = 100

Exposure Scenario	AR (lb ai/A)	TC (cm^2/hr)	Exposure Duration (hrs/day)	Dermal dose (mg/kg/day)	Dermal MOE
Adult Golfers	0.25	500	4	0.00024	5200
Child Golfer		500	4	0.00043	2900

[1] Application rates are based on maximum values based on proposed label.
[2] TTR or DFR (mg/cm^2) = Application Rate (lb ai/A) x CF (4.54E+5 mg/lb) x CF (2.47E-8 A/ cm^2) x 5% (initial fraction of ai retained on turf) Application rates are based
[3] TC cm^2/hr = Transfer coefficients and associated activities (ExpoSAC Policy Memo #003.1)
[4] Dermal Dose (mg/kg/day) = TTR (mg/cm^2) x TC (cm^2/hr) x 4 (hrs/day) x 6% DAF/70 kg-adult, 39 kg-child (body weight)
[8] Dermal MOE = short-term endpoint for dermal (NOAEL 1.25 mkd)/Daily Dermal Dose

7.0 AGGREGATE EXPOSURE AND RISK ASSESSMENT

In accordance with the FQPA, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major routes: oral, dermal, and inhalation. There are three sources for these types of exposures: food, drinking water, and residential uses. In an aggregate assessment, risks from relevant sources are added together and compared to a level of concern. Since a common effect has been identified for assessment of short-term oral, dermal, and inhalation exposures (changes in body weights and body-weight gains) for difenoconazole, the short-term aggregate risk assessment combines exposure from food, water, and residential sources. The acute and chronic exposure estimates

from the dietary exposure analyses represent aggregate risk for acute and chronic exposures.

7.1 Short-Term Aggregate Risk to Residential Applicators

Short term aggregate exposure takes into account residential exposure plus average exposure levels to food and water (considered to be a background exposure level). The short term aggregate risk for residential handlers is the estimated risk associated with combined risks from average food and drinking water exposures and dermal and inhalation exposures to adult applicators. Short term aggregate risk estimates for residential handlers are provided in Table 11 aggregates the short-term risk for adults from residential handler exposure, and average food and water exposure (as a background). The lowest aggregate MOE is 260, which is greater than the target MOE of 100 and therefore not of concern

Table 15: Estimated Difenoconazole Short-term Aggregate Risk to Adults from Residential Handler Activities

Exposure Scenario	Target MOE	Route of Exposure	Daily dose	NOAELs	MOE at Day 0	Combined MOE[4]
Average Food and Water (As background)	N/A	Food and water	0.0018	1.25	700 [2]	NA
Hose End Sprayer - Ornamentals	100 [1]	Dermal and Inhalation	0.0022		575 [3]	310
Handheld Pump Spray - Ornamentals			0.0031		400	260
Hose End Sprayer – Flower Gardens			0.0019		660	340
Handheld Pump Spray – Flower Gardens			0.0021		590	320

[1] Target MOE= 100, Developmental rat- increased incidence of rudimentary risks. NOAEL = 0.96
[2] MOE food and water = [(short-term oral NOAEL)/(chronic dietary exposure)]
[3] MOE dermal and inhalation = [(short -term NOAEL)/(high-end inhalation and dermal residential exposure)]
[4] Aggregate Combined MOE (food, water, and residential) = 1÷ [(1÷MOE food and water) + (1÷MOE handler inhalation and dermal)].

7.2 Short-Term Aggregate Risk for Residential Post-Application Exposure

Table 16 aggregates the short-term risk for adults from residential post application, and average food and water exposure. The highest post application exposure from residential use on turf was used in the short term aggregate. The aggregate MOE is 460, which is greater than the target MOE of 100. This aggregate exposure assessment is considered very conservative because the assumptions used for each of the scenarios separately are already high end (i.e., time spent outdoors, dislodgeable residues).

Table 16: Estimated Difenoconazole Short-term Aggregate Risk from Residential Post-Application Activities						
Exposure Scenario	Target MOE	Route of Exposure	Exposure or Daily dose	NOAELs	MOE at Day 0	Combined MOE[4]
Average Food and Water Adult	N/A	Food and water	0.0018	1.25	700 [2]	NA
Average Food and Water Child			0.0023		540	
Adult Golfer	100 [1]	Dermal	0.00024		5200 [3]	600
Child Golfer			0.00043		2900	460

[1] Target MOE= 100, Developmental rat- increased incidence of rudimentary risks. NOAEL = 30
[2] MOE food and water = [(short-term oral NOAEL)/(chronic dietary exposure)]
[3] MOE dermal = [(short -term dermal NOAEL)/(high-end dermal residential exposure)]
[4] Aggregate Combined MOE (food, water, and residential) = 1÷ [(1÷MOE food and water) + (1÷MOE post appl. dermal)].

8.0 OCCUPATIONAL EXPOSURE AND RISK

Occupational handler and post-application exposure scenarios are assessed for proposed new uses on strawberry, carrot, chickpeas, soybean, stone fruit, and turf and existing uses on fruit and nut commodities and ornamentals. Based on the product labels and information provided by the registrant, short- and intermediate-term exposures are assessed for occupational handlers and post-application activities. Dermal and inhalation exposures to workers are aggregated for difenoconazole because the PODs for these routes are based on common toxicological effects.

8.1 Occupational Handler Exposure

The term "handler" applies to individuals who mix, load, and apply the pesticide product. There is a potential for exposure to difenoconazole during mixing, loading, and application activities through the dermal and inhalation routes. Difenoconazole products are applied using aerial, groundboom, chemigation and handheld sprayers.

8.1.1 Occupational Handler Exposure Scenarios

The following handler exposure scenarios evaluated for this assessment are based on information provided in the proposed and existing labels.

8.1.1.1 Foliar Spray

- Open mixing/loading liquid formulation for groundboom, aerial, chemigation, and airblast application to food crops
- Open mixing/loading/applying with groundboom, LCO Handgun, high pressure handwand, low pressure handwand, backpack sprayer equipment to ornamentals and turf
- Applying with aerial, groundboom, airblast sprayer equipment to food crops and/or ornamentals
- Flagging for aerial application to food crops

8.1.1.2 Seed Treatment

- Loading/Applying - Flowable concentrate for Seed treatment applications (single layer clothing with gloves).
- Sewing - Flowable concentrate for Seed treatment applications (single layer clothing with no gloves/ "Baseline").
- Bagging - Flowable concentrate for Seed treatment applications (single layer clothing with no gloves/ "Baseline").
- Multiple Activities - Flowable concentrate for Seed treatment applications (single layer clothing with gloves).

8.1.2 Occupational Handler Exposure Data

No chemical-specific handler exposure data were submitted in support of this registration. When chemical-specific monitoring data are not available, it is HEDs policy to use data from the Pesticide Handlers Exposure Database (PHED) to assess handler exposures for regulatory actions (HED Exposure SOP #7, 1/28/99).

8.1.3 Occupational Handler Exposure Assumptions

- Average body weight of an adult handler is 70 kg.
- Dermal Absorption Factor = 6%
- Exposure duration is short-term (1- 30 days) and intermediate-term (1-6 months)
- Maximum label application rates:
  - 0.125 lb ai/A for citrus
  - 0.114 lb ai A for soybean, strawberry, carrot, chickpeas, stone fruit
  - 0.13 lb ai/A; 2.08 lb ai/gal for ornamentals
  - 0.25 lb ai/A; 1.05 lb ai/gal for golf course turf
  - 0.025 lb ai/100 lb seed for barley and sweet corn seed
  - 0.0305 lb ai/100 lb seed for cotton seed
- Area treated:
  - 1200 acres per day for aerial application to soy bean crop
  - 350 acres per day for aerial application to fruit and nut crop
  - 80 acres per day for groundboom application to fruit and nut crop
  - 40 acres per day for groundboom application to golf course turf and airblast for citrus
  - 100 acres per day for LCO handgun applications to golf course turf
  - 80 acres per day for groundboom application (sweet corn)
  - 5 acres per day for handheld spray sprayer applications to golf course turf
- Amount of seed treated:
  - 718000 lbs/day for barley
  - 194000 lbs/day for sweet corn
  - 160000 lbs/day for cotton

8.1.4 Occupational Handler Exposure and Risk

Exposure and risk estimates indicate risks are not of concern for occupational handler activities for the existing and proposed new uses (i.e., MOEs > 100). A summary of occupational handler exposure and risk calculations, assumptions, and results is provided in Tables 17, 18 and 19.

Table 17. Estimated Exposure & MOEs for Short- and Intermediate-Term Occupational Handler - Exposure Existing Uses of Difenoconazole on Crops and Ornamentals LOC/MOE = 100

Exposure Scenario	Unit Exposure[1]			Appl Rate (lb ai/A or Gal)[2]	Area Treated (A/ or Gal/ day)[3]	Crop	ST & IT Dose (mg/kg/day)[4]			ST & IT MOEs			Agg dose (mg/kg/day)		Agg MOE[5]	
	Inhal (ug/lb ai)	Dermal					Dermal		Inhal	Dermal		Inhal	BL	BL + Glove	BL	BL + Glove
		BL (mg/lb ai)	BL + Glove (mg/lb ai)				BL	BL + Glove		BL	BL+ Glove					
Mixing/Loading - Liquid																
groundboom	1.2	2.9	0.023	0.125	80	citrus	0.0002	0.0249	0.0002	50	6300	7300	0.0250	0.0004	50	3400
aerial chemigation	1.2	2.9	0.023	0.125	350	citrus	0.0008	0.1088	0.0009	10	1450	1700	0.1095	0.0016	11	800
aerial application	1.2	2.9	0.023	0.114	1200	soy bean	0.0023	0.3400	0.0027	5	500	500	0.3424	0.0050	4	250
airblast	1.2	2.9	0.023	0.125	40	citrus	0.0001	0.0124	0.0001	100	13000	15000	0.0125	0.0002	100	6800
Applying Liquid																
groundboom	0.74	0.014	NA	0.125	80	citrus	0.0001	0.0001	NA	10417	NA	11800	0.0002	NA	5538	NA
aerial	0.07	0.005	NA	0.125	350	citrus	0.0000	0.0002	NA	6667	NA	29000	0.0002	NA	5435	NA
airblast	4.5	0.36	0.24	0.125	40	citrus	0.0003	0.0015	0.0010	810	1200	4000	0.0019	0.0014	670	1000
Flagging																
aerial	0.35	0.011	0.012	0.125	350	soy	0.0005	0.0004	0.0002	3030	2800	5700	0.0007	0.0006	1980	1900
Mixing/Loading/Applying - Liquid																
groundboom	1.3	0.37	0.057	0.13	40	Ornamentals	0.0001	0.0016	0.0003	758	4900	13000	0.0017	0.0004	716	3600
LCO handgun	1.8	NA	0.45	0.13	5		0.0000	NA	0.0003	NA	5000	75000	NA	0.0003	NA	4700
low pressure handwand	30	100	0.43	0.003	40 G		0.0103	0.0000	0.0001	122	28000	24000	0.0130	0.0001	121	13000
backpack sprayer	30	NA	2.5	0.003	40 G		NA	0.0003	0.0001	NA	5000	24000	NA	0.0003	NA	4100

[1] Baseline (BL) and personal protective equipment (PPE) unit exposure values are reported in the PHED Surrogate Exposure Guide dated August 1998: Groundboom and aerial mixer/loader unit exposures are the same for baseline PPE and Gloves

[2] Application rates based on labels .

[3] Amount treated based on information provided ExpoSAC Policy 9

[4] Dermal dose (mg/kg/event) = [unit dermal exposure (mg/lb ai) * application rate (lb ai/A) * Amount treated*DAF / body weight (70 kg)].
Inhalation dose (mg/kg/event) = [unit exposure (kg/lb ai) * (1mg/1000 kg) conversion * appl. rate (lb ai/lbs seed) * Amount treated / body weight (70 kg)].

[5] Agg MOE = 1/(1/Dermal MOE + 1/Inhalation MOE).

Table 18. Estimated Exposure & MOEs for Short- and Intermediate-Term Occupational Handler Exposure – Existing Use of Difenoconazole for Seed Treatment Dermal and Inhalation LOC/MOE = 100

Personal Protective Equipment[1]	Inhal Unit Exposure (ug/lb ai)[2]	Dermal Unit Exposure (mg/lb ai)[3]	Crop	App Rate (lb ai/lb seed)[4]	Amt Treated (lb seed/day)[5]	Inhal Dose (mg/kg/d)[6]	Inhal MOE	Dermal Dose[7]	Derm MOE	Agg Dose[8]	Agg MOE[9]
Loader/Applicator											
Single layer gloves	0.34	0.023	barley	0.000244	718000	0.00099	10100	0.00345	2900	0.00445	280
Single layer gloves	0.34	0.023	Sweet Corn	0.000244	194000	0.00027	37300	0.00093	10700	0.00120	1000
Single layer gloves	0.34	0.023	cotton	0.000305	160000	0.00028	36100	0.00096	10400	0.00124	1000
Sewer											
Single layer gloves	0.23	0.0062	barley	0.000244	718000	0.00067	14900	0.00093	10700	0.00160	780
Single layer gloves	0.23	0.0062	Sweet Corn	0.000244	194000	0.00018	55100	0.00025	40000	0.00043	2900
Single layer gloves	0.23	0.0062	cotton	0.000305	160000	0.00019	53500	0.00026	39000	0.00045	2800
Bagger											
Single layer no gloves	0.16	0.0091	barley	0.000244	718000	0.00047	21400	0.00137	7300	0.00183	680
Single layer no gloves	0.16	0.0091	Sweet Corn	0.000244	194000	0.00013	79200	0.00037	27000	0.00050	2500
Single layer no gloves	0.16	0.0091	cotton	0.000305	160000	0.00013	76800	0.00038	26000	0.00051	2500
Multiple Activities											
Single layer no gloves	1.6	0.042	barley	0.000244	718000	0.00467	2100	0.00631	1600	0.01098	900
Single layer no gloves	1.6	0.042	Sweet Corn	0.000244	194000	0.00126	7900	0.00170	5900	0.00297	3400
Single layer no gloves	1.6	0.042	cotton	0.000305	160000	0.00130	7700	0.00176	5700	0.00306	3300
Planting											
Single layer gloves	3.4	0.25	barley	0.000244	718000	0.00993	1000	0.03754	270	0.04747	200
Single layer gloves	3.4	0.25	Sweet Corn	0.000244	194000	0.00268	3700	0.01014	990	0.01283	780
Single layer gloves	3.4	0.25	cotton	0.000305	160000	0.00277	3600	0.01046	960	0.01322	760

[1] PPE (Personal Protection Equipment)
[2] Inhalation Exposure is based on a Baseline exposure scenario (no respiratory protection).
[3] Dermal Unit Exposure is characterized with existing table.
[4] Application rates are based on label specific information
[5] Amount/Seed treated values are based on ExpoSAC SOP
[6] Inhalation dose (mg/kg/event) = [unit exposure (kg/lb ai) * (1mg/1000 kg) conversion * appl. rate (lb ai/lbs seed) * Amount treated / body weight (60 kg)].
[7] Dermal dose (mg/kg/event) = [unit dermal exposure (mg/lb ai) * dermal absorption (0.6) * application rate (lb ai/lb seed) * Amount treated / body weight (70 kg)].
[8] Agg does = dermal dose + inhalation dose.
[9] Agg MOE = NOAEL (1.25 mg/kg/d) / combined inhalation and dermal dose. MOE = 100.
[10] Gloves used for loading only.

Table 19. Estimated Exposure & MOEs for Short- and Intermediate-Term Occupational Handler Exposure - New Uses of Difenoconazole on Turf LOC/MOE = 100

Exposure Scenario*	Unit Exposure[1]			Appl Rate (lb ai/A or Gal)[2]	Area Treated (A/ or Gal/ day)[3]	Crop	ST & IT Dose (mg/kg/day) [4]			ST & IT MOEs			Agg dose (mg/kg/day)		Agg MOE[5]	
	Inhal (ug/lb ai)	Dermal					Dermal		Inhal	Dermal		Inhal	BL	BL + Glove	BL	BL + Glove
		BL	BL + Glove				BL	BL + Glove		BL	BL+ Glove					
		(mg/lb ai)														
Mixing/Loading - Liquid																
groundboom	1.2	2.9	0.023	0.25	40	turf	0.0249	0.0002	0.0002	50	6300	7300	0.0250	0.0004	50	3400
LCO Handgun	0.74	2.9	0.23	0.25	100		0.0621	0.0005	0.0003	20	250	4700	0.0624	0.0008	20	1700
Applying Liquid																
groundboom	0.74	0.014	NA	0.25	40	turf	0.0001	NA	0.0001	10400	NA	11800	10417	NA	5500	NA
LCO Handgun	1.4	NA	0.34	0.25	5		NA	0.0004	0.0000	NA	3400	50000	NA	0.0004	NA	3200
Mixing/Loading/Applying - Liquid																
groundboom	1.3	0.37	0.057	0.25	40	turf	0.0032	0.0005	0.0002	390	2600	6700	0.0034	0.0007	370	1900
LCO handgun	1.8	NA	0.45	0.25	5		0.0005	NA	0.0003	NA	2600	39000	NA	0.0005	NA	2400
low pressure handwand	30	100	0.43	0.006	40 G		0.0206	0.0001	0.0001	61	14000	12500	0.0207	0.0002	60	6500
Backpack Sprayer	30	NA	2.5	0.006	40 G		0.0180	NA	0.0005	NA	2400	12200	NA	0.0006	NA	2000

[1] Baseline and PPE unit exposure values are reported in the PHED Surrogate Exposure Guide dated August 1998: Groundboom and aerial mixer/loader unit exposures are the same for baseline PPE and Gloves

[2] Application rates based on labels .

[3] Amount treated based on information provided ExpoSAC Policy 9

[4] Dermal dose (mg/kg/event) = [unit dermal exposure (mg/lb ai) * application rate (lb ai/A) * Amount treated / body weight (70 kg)].

[5] Inhalation dose (mg/kg/event) = [unit exposure (kg/lb ai) * (1mg/1000 kg) conversion * appl. rate * Amount treated *DAF/ body weight (70 kg)].

[6] Agg MOE = 1/(1/Dermal MOE + 1/Inhalation MOE).

8.2 Occupational Post-Application Exposure

HED uses the term "post-application" to describe those individuals who can be exposed to pesticides after entering areas previously treated with pesticides and performing certain tasks or activities (also often referred to as reentry exposure). The specific activity, the nature of the crop or target that was treated, and the how chemical residues degrade in the environment can cause exposure levels to differ over time. Each of these factors is considered in the post-application exposure assessment. Difenoconazole is applied post-bloom.

Post-application exposures are expected to occur primarily via the dermal route. Based on the Agency's current practices, a quantitative post application inhalation exposure assessment was not performed for difenoconazole. However, volatilization of pesticides may be a potential source of post application inhalation exposure to individuals nearby to pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 and is in the process of evaluating the SAP report. The Agency may, as appropriate, develop policies and procedures to identify the need for and, subsequently, the way to incorporate post application inhalation exposure into the Agency's risk assessments. If new policies or procedures are put

into place, the Agency may revisit the need for a quantitative post application inhalation exposure assessment.

8.2.1 Occupational Post-Application Exposure Scenarios

There are no compound specific data with which to estimate post-application exposures to agricultural workers. Estimates of post-application re-entry exposure to agricultural workers are based upon the EXPOSAC Standard Operating Procedures (SOPs) (3.1, Reference 4). This SOP lists a number of possible post-application agricultural activities for the proposed crop uses that might result in post-application.

The following post-application exposure scenarios were assessed for proposed post-emergence uses of difenoconazole.

- Deciduous Trees; thinning, harvesting, pruning, training, tying
- Tree Nuts; harvesting/poling, pruning, thinning
- Root Vegetables; hand harvesting
- Cucurbit Vegetables; hand harvesting, pulling, leaf thinning, thinning, turning
- Fruiting Vegetables; hand harvesting, pruning, staking, tying
- Brassica; hand harvesting, irrigation, pruning, topping, tying mature plants
- Leafy Vegetables; hand harvesting, pruning, and thinning mature plants
- Vine/Trelis Crops (Grapes); hand harvest, leaf pulling, thinning, pruning, training/tying grapes
- Low/Medium Height Field Row Crops (Soybean); hand harvesting

In accordance with the Worker Protection Standard (WPS), a 12-hr restricted entry interval (REI) is required for chemicals classified under Toxicity Category III/IV.

8.2.2 Occupational Post-application Exposure Data

No chemical-specific handler exposure data were submitted in support of this registration. Therefore, agricultural transfer coefficients used for this assessment are taken from HED's Science Advisory Council for Exposure Policy on Agricultural Transfer Coefficients (SOP # 003.1, 8/7/2000).

8.2.3 Occupational Post Application Exposure Assumptions

- Average body weight of an adult handler is 70 kg.
- Dermal Absorption Factor = 6%
- Exposure duration:
  - short-term (1- 30 days)
- Maximum label application rates:
  - 0.125 lb ai/A for citrus
  - 0.114 lb ai /A for all other existing and proposed uses on food crops
  - 0.25 lb ai/a for golf course turf

- Transfer Coefficients:
  - 3000 cm^2/hour for thinning deciduous tree crop
  - 2500 cm^2/hour for
    - harvesting, poling, pruning, thinning tree nut crop
    - hand harvesting root vegetable crop
    - hand harvesting, pulling, leaf thinning, thinning, turning cucurbit vegetable crop
    - hand harvesting, pruning, and thinning mature leafy vegetable plants
    - hand harvesting soybean crop
  - 1000 cm^2/hour for hand harvesting, pruning, staking, tying fruiting vegetable crop
  - 5000 cm^2/hour for hand harvest, leaf pulling, thinning, pruning, training/tying grapes
- Initial fraction of ai retained on foliage is 20%
- Exposure is assumed to occur on the day of application (day 0)

8.2.4 Occupational Post-Application Exposure and Risk Estimates

Exposure estimates indicate that post-application risks are not of concern (MOEs > 100). A summary of post-application exposure and risk calculations, assumptions, and results is provided in Table 20.

Table 20. Estimated Difenoconazole Exposure & MOEs for Occupational Post-Application Exposure

Exposure Scenario	Activity	App Rate (lb ai/A) [1]	TTR/DFR (mg/cm^2) [2]	TC (cm^2/hr) [3]	Exposure Duration (hrs/day)	Dermal dose (mg/kg/day) [4]	MOE [5]
Deciduous Tree (Citrus)	thinning	0.125	0.00028	3000	8	0.0058	200
Tree Nut	harvesting, poling, pruning, thinning	0.114	0.00026	1500		0.0027	500
Fruiting Vegetable	hand harvesting, pruning, staking, tying			1000		0.0018	700
Grape	hand harvest, leaf pulling, thinning, pruning, training/tying			5000		0.0088	150
Root vegetable	hand harvesting			2500		0.0044	280
Cucurbit vegetable	hand harvesting, pulling, leaf thinning, thinning, turning						
Leafy vegetable	harvesting, pruning, thinning						
Soybean	hand harvesting						

[1] Application rates are based on maximum values based on proposed label.
[2] DFR (mg/cm^2) = Dislodgeable Foliar Residues corresponding to day 0. Application Rate (lb ai/A) x CF (4.54E+5 mg/lb) x CF (2.47E-8 A/ cm^2) x 20% (initial fraction of ai retained on foliage)
[3] TC cm^2/hr = Transfer coefficients and associated activities (ExpoSAC Policy Memo #003.1)
[4] Dermal Dose (mg/kg/day) = DFR (mg/cm^2) x TC (cm^2/hr) x 8 (hrs/day) x DAF/ Body weight (70 kg).
[5] Dermal MOE = short-term endpoint for dermal (NOAEL 1.25 mg/kg/day x 6% (DAF)) /Dermal Dose

8.2.5 Spray Drift

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for difenoconazole. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices, and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast, and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

9.0 CUMULATIVE RISK

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether difenoconazole has a common mechanism of toxicity with other substances. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to difenoconazole and any other substances and, difenoconazole does not appear to produce a toxic metabolite produced by other substances which have tolerances in the U. S. For the purposes of this tolerance reassessment action, therefore, EPA has not assumed that difenoconazole has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's OPP concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/fedrgstr/EPA_PEST/2002/January/Day_16/.

10.0 REFERENCES

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D378938, 2/23/11

Common Triazole Metabolites: Updated Dietary (Food + Water) Exposure and Risk Assessment to Address The Amended Difenoconazole Section 3 Registration to Add Uses on Carrots, Chickpeas, Soybeans, Stone Fruits (Group 12), Strawberries, and Turnip Greens and The Tetraconazole Section 3 Registration to Add Field Corn, Pop Corn, Crop Subgroup 13-07F, and Crop Subgroup 13-07G (except cranberry). T. Morton, D386652, 2/16/11

Difenoconazole: Occupational and Residential Exposure Assessment for the Proposed New Use of Difenoconazole on Proposed New Uses of Difenoconazole on Strawberry, Carrot, Chickpeas, Soybean, Stone Fruit: Group 12 and Golf Course Turfgrass B. Daiss, D371037 2/24/11

Difenoconazole (Parent Only) Drinking Water Assessment in Support of New Use Registration Action for Golf Course Turf. I. Maher, D371044, 6/1/10

Drinking Water Exposure Assessment to Establish a Tolerance of parent difenoconazole on carrot, chickpeas, soybean, stone fruits, and strawberry. F. Khan, D378946, 9/27/10

Difenoconazole. Request for Restatement of 1994 EPA Cancer Classification and Risk Assessment Approach Using Current Terminology. P.V. Shah, D 318039, 3/1/07

APPENDICES

A. TOXICOLOGY DATA SUMMARY

A.1 Guideline Data Requirements

Table 1. Guideline Data Requirements

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	yes	yes
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5900	Mutagenicity—Other Genotoxic Effects		
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90-Day Neuro. Screening Battery (rat)	yes	yes
870.6300	Develop. Neuro	no	-
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	-	-
870.7800	Dermal Penetration	no	-

A.2 Toxicity Profiles

Table 1. Acute Toxicity Profile – Difenoconazole				
Guideline No.	**Study Type**	**MRID No.**	**Results**	**Toxicity Category**
870.1100	Acute oral	42090006	LD_{50} = 1450 mg/kg	III
870.1200	Acute dermal	42090007	LD_{50} > 2010 mg/kg	III
870.1300	Acute inhalation	42090008	LC_{50} > 3.3 mg/L	III
870.2400	Eye irritation	42090009	Mild irritation reversible in 7 days	III
870.2500	Dermal irritation	40789807	Slight irritation	IV
870.2600	Skin sensitization	42090011, 42710004	Negative	N/A

Table 2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (rat)	42090022 (1987) Acceptable/guideline 0, 20, 200, 750, 1500 or 3000 ppm 0, 1, 10, 37.5, 75 and 150 mg/kg/d	NOAEL = 20 ppm (1 mg/kg/day) LOAEL = 200 ppm (10 mg/kg/day) based on the 10% decrease in body weight in the 200 ppm females (as well as a negative trend in feed consumption) and Increases in absolute liver weights in both sexes
870.3100	90-Day oral toxicity (mouse)	42090021 (1987) Minimum/guideline 0, 20, 200, 2500, 7500 or 15,000 ppm M: 0, 2.9, 30.8, 383.6, 1125 and 2250 mg/kg/d F: 0, 4.1, 41.5, 558.9, 1125 and 2250 mg/kg/d	NOAEL = 20 ppm (2.9 mg/kg/day) LOAEL = 200 ppm (30.8 mg/kg/day) based on body weight changes & liver histopathology.
870.3150	26-Week oral toxicity	42090012 (1987) Minimum/ guideline 0, 100, 1000, 3000 or 6000 ppm M: 0, 3.6, 31.3, 96.6 and 157.8 mg/kg/d F: 0, 3.4, 34.8, 110.6 and 203.7 mg/kg/d	NOAEL = 3000 ppm (31.3 mg/kg/day in males/34.8 mg/kg/day in females) LOAEL = 6000 ppm (96.6 mg/kg/day in males/110.6 mg/kg/day in females), based primarily on microscopic examination of CGA 169374-related lenticular cataracts.
870.3200	21/28-Day dermal toxicity (rat)	42090013 (1987) Minimum/ guideline 0, 10, 100 and 1000 mg/kg/d	NOAEL = 10 mg/kg/day LOAEL = 100 mg/kg/day based on statistically significant decrements in body weight, body weight gain, and food consumption.
870.3200	21/28-Day dermal toxicity (rat)	46950310 (2000) Acceptable/ guideline 0, 10, 100 and 1000 mg/kg/d	NOAEL (systemic) = 1000 mg/kg/day LOAEL (systemic) was not determined. NOAEL (dermal) = 100 mg/kg/day LOAEL (dermal) = 1000 mg/kg/day based on hyperkeratosis at the skin application site.

Table 2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700a	Prenatal developmental in (rat)	42090016, 42710007 (1987) Minimum/ guideline 0, 2, 20, 100 or 200 mg/kg/d from GD 6-15 (nominal doses differed widely from theoretical, this required altering NOAEL/LOAEL values)	Maternal NOAEL = 16 mg/kg/day LOAEL = 85 mg/kg/day based on decreased body weight gain and food consumption. Developmental NOAEL = 85 mg/kg/day LOAEL = 171 mg/kg/day based on alterations in fetal ossification.
870.3700b	Prenatal developmental in (rabbit)	42090017, 42710008 (1987) Minimum/ guideline 0, 1, 25 or 75 mg/kg/d from GD 7-19	Maternal NOAEL = 25 mg/kg/day LOAEL = 75 mg/kg/day based on decreased body weight gain and food consumption. Developmental NOAEL = 25 mg/kg/day LOAEL = 75 mg/kg/day based on nonsignificant increases in postimplantation loss and resorptions/doe and a significant decrease in fetal weight.
870.3800	Reproduction and fertility effects (rat)	42090018 (1988) Minimum/ guideline 0, 25, 250 or 2500 ppm 0, 1.25, 12.5 and 125 mg/kg/d	Parental/Systemic NOAEL = 25 ppm (1.25 mg/kg/day) LOAEL = 250 ppm (12.5 mg/kg/day) based on reductions (statistically nonsignificant) in body weight gain which appear to be part of a dose-related trend days 70-77 prior to mating, days 0-7 of gestation, and days 7-14 of lactation Offspring NOAEL = 25 ppm (1.25 mg/kg/day) LOAEL = 250 ppm (12.5 mg/kg/day) based on a significant reduction in the body weight of F1 male pups at day 21 in the 250 ppm group.
870.4100b	Chronic toxicity (dog)	42090012, 42710005 (1988) Minimum/ guideline 0, 20, 100, 500 or 1500 ppm M: 0, 0.71, 3.4, 16.4 and 51.2 mg/kg/d F: 0, 0.63, 3.7, 19.4 and 44.3 mg/kg/d	NOAEL = 100 ppm (3.4 mg/kg/day in males/3.7 mg/kg/day in females) LOAEL = 500 ppm (16.4 mg/kg/day in males/19.4 mg/kg/day in females), based on significant inhibition of body weight gain in females.
870.4200	Carcinogenicity (rat)	42090019, 42710010 (1989) Minimum/ guideline 0, 10, 20, 500 or 2500 ppm M: o, 0.48, 0.96, 24.12 and 123.7 mg/kg/d F: 0, 0.64, 1.27, 32.79 and 169.6 mg/kg/d	NOAEL = 20 ppm (0.96 mg/kg/day in males/1.27 mg/kg/day in females) LOAEL = 500 ppm (24.1 mg/kg/day in males/ 32.8 mg/kg/day in females) based on reductions in cumulative body weight gains in the 500 and 2500 ppm groups. No evidence of carcinogenicity
870.4300	Carcinogenicity (mouse)	42090015, 42710006 (1989) Minimum/ guideline 0, 10, 30, 300, 2500 or 3000 ppm M: 0, 1.51, 4.65, 46.29, 423.1 and 818.9 mg/kg/d F: 0, 1.9, 5.63, 57.79 and 512.6 mg/kg/d	NOAEL = 30 ppm (4.7 mg/kg/day in males/5.6 mg/kg/day in females) LOAEL = 300 ppm (46.3 mg/kg/day in males/57.8 mg/kg/day in females) based on reductions in the cumulative body weight gains and hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis in the 300, 2500 & 4500 ppm groups. Evidence of carcinogenicity (liver adenoma/carcinoma in both sexes)

Table 2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5100	*In vitro* bacterial gene mutation *(Salmonella typhimurium/ E. coli)*/ mammalian activation gene mutation assay	42090019, 42710010 (1989) Minimum/ guideline 340 - 5447 µg/plate; 85 - 1362 µg/plate (repeat assay with TA1537 and TA98)	There were sufficient and valid data to conclude that CGA 169374 technical was negative in the microbial gene mutation assay.
870.5300	*in vitro* mammalian cell gene mutation assay in mouse lymphoma cells	42090024 (1986) Unacceptable/ guideline	No conclusion can be reached from the three nonactivated and two S9 activated mouse lymphoma forward mutation assays conducted with difenoconazole technical. The study was seriously compromised.
870.5375	*In vitro* Mammalian Cytogenetics (chromosomal aberrations) assay in Chinese hamster CHO cells	46950319 (2001) Acceptable/ guideline 0, 21.99, 27.49, or 34.36 µg/mL (-S9) 0, 34.36, 53.69 or 67.11 µg/mL (+S9)	There was evidence of a weak induction of structural chromosomal aberrations over background in the presence of S9-mix.
870.5375	*In vitro* Mammalian Cytogenetics (chromosomal aberrations) assay in Chinese hamster CHO cells	46950321 (2001) Acceptable/ guideline 0, 26.3, 39.5 or 59.3 µg/mL (-S9) 0, 11.7 or 17.6 µg/mL (+S9)	There was evidence of a weak induction of structural chromosomal aberrations over background.
870.5375	*In vitro* Mammalian Cytogenetics (chromosomal aberrations) assay in human lymphocytes	46950323 (2001) Acceptable/ guideline 0, 5, 30 or 75 µg/mL (-S9) 0, 5, 30 or 62 µg/mL (+S9)	There was no evidence of structural chromosomal aberrations induced over background.
870.5385	*In vivo* mammalian chromosomal aberration test Assay in Mice	42090023 (1986) Unacceptable/guideline 250, 500 or 1000 mg/kg	There was no evidence of a cytotoxic effect on the target organ or significant increase in the frequency of nuclear anomalies (micronuclei). However, the study was compromised.
870.5395	*In vivo* mammalian cytogenetics - erythrocyte micronucleus assay in mice	41710011 (1992) Acceptable/guideline Doses up to 1600 mg/kg	Mice bone marrow - No increase in micronucleated polychromatic erythrocytes occurred with CGA-1 69374 (91.2% a.i).

Table 2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	4210012 (1992) Acceptable/ guideline Doses up to 50 µg/mL	CGA-i69374 tech. (92.2% a.i.) was considered to be negative in the unscheduled DNA synthesis assay in rat primary hepatocytes as measured by an autoradiographic method at concentrations up to 50.0 µg/mL.
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	42090027 (1985) Unacceptable/ guideline 0.25-31.25 µg/mL	No conclusion can be reached from the unscheduled DNA synthesis (UDS) primary rat hepatocyte assay conducted with difenoconazole technical at concentrations ranging from 0.25 to 31.25 µg /mL. The sensitivity of the study was severely compromised.
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	42090026 (1985) Unacceptable/ guideline 0.08-10 µg/mL	No conclusion can be reached from the unscheduled DNA synthesis (UDS) human fibroblast assay conducted with difenoconazole tech. at conc. ranging from 0.08 to 10 µg /mL.
870.6200a	Acute neurotoxicity screening battery	46950327 (2006) Acceptable/ guideline 0, 25, 200 or 2000 mg/kg/d	NOAEL (M) = 25 mg/kg/day LOAEL (M) = 200 mg/kg/day based on reduced fore-limb grip strength in males on day 1 and increased motor activity on Day 1. NOAEL (F) = 200 mg/kg/day LOAEL (F) = 2000 mg/kg/day based on decreased body weight, the following clinical signs: upward curvature of the spine, tip-toe gait, decreased activity, piloerection and sides pinched in and decreased motor activity.
870.6200b	Subchronic neurotoxicity screening battery	46950329 (2006) Acceptable/ guideline 0, 40, 250, or 1500 ppm M; 0, 2.8, 17.3 or 107.0 mg/kg/d F: 0, 3.2, 19.5, or 120.2 mg/kg/d	NOAEL (M) = 40 ppm (2.8 mg/kg/day) LOAEL (M) = 250 ppm (17.3 mg/kg/day) based on decreased hind limb strength. NOAEL (F) = 250 ppm (19.5 mg/kg/day) LOAEL (F) = 1500 (120.2 mg/kg/day) based on decreased body weight, body weight gain and food efficiency.
870.7485	Metabolism and pharmacokinetics (rat)	42090028 (1990) Acceptable/ guideline 14 daily doses of 0.5 or 300 mg/kg	The absorption, distribution, metabolism, and excretion of CGA 169374 were studied in groups of male and female Sprague-Dawley rats. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg [^{14}C]CGA-169374, or 0.5 mg/kg unlabeled GGA-169374 by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C)CGA-169374 on day 15. The test compound was labeled with C^{14} at either the phenyl or triazole ring.

Table 2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485	Metabolism and pharmacokinetics (rat)	42090031 (1988) Acceptable/ guideline 0.5 or 300 mg/kg	These studies indicate that distribution, metabolism, and elimination of CGA-169374 were not sex related. There was a slight dose difference in the metabolism and elimination of CGA-169374. In phenyl and triazole labeling studies, fecal excretion of radioactivity was higher in the high dose animals compared to the low dose animals, and an additional metabolite was found in the feces of the high dose animals compared to the low dose animals. There was no major difference in the distribution and excretion of radioactivity with labeling at the phenyl and triazole ring positions, however, there were some different metabolites identified. The studies also showed that administration of 0.5 and 300 mg/kg CGA- 169314 did not induce any treatment related clinical effects.
870.7485	Metabolism and pharmacokinetics (rat)	420710013, 42710014 (1990) Acceptable/ guideline 0.5 or 300 mg/kg	These two studies described the absorption, distribution, and excretion as the pharmacokinetics and isolated and identified urinary metabolites. Issues raised in the previous supplementary studies were answered. In conjunction with these studies, the previous studies are upgraded.
870.7485	Metabolism and pharmacokinetics (rat)	42090029 (1987) Acceptable/ guideline	[14C]CGA-169374 was rapidly and extensively distributed. metabolized, and excreted in rats for all dosing regimens. The extent of absorption is undetermined pending determination of the extent of biliary excretion. The 4-day recoveries were 97.4-107.75% of the administered dose for all dosing groups. The elimination of radioactivity in the feces (78.06-94.61% of administered dose) and urine (8.48-21.86%) were almost comparable for all oral dose groups, with slightly higher radioactivity found in the feces of the high dose group than the low dose groups. This was probably due to biliary excretion, poor absorption or saturation of the metabolic pathway. The radioactivity In the blood peaked at about 24-48 hours for all dosing groups. Half-lives of elimination appear to be approximately 20 hours for the low dose groups and 33 - 48 hours for the high dose group. The study results also indicate that CGA-1 69374 and/or its metabolites do not bioaccumulate to an appreciable extent following oral exposure since all the tissues contained negligible levels (<1%) of radioactivity 7 days postexposure.

Table 2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485	Metabolism and pharmacokinetics (rat)	42090030 (1987) Acceptable/ guideline	The metabolism of CGA-169374 appears to be extensive because the metabolites accounted for most of the recovered radioactivity in the excreta. Three major metabolites were identified in the feces (i.e., A, B, and C). Two of the metabolites were separated into isomers (i.e., A1, A2, B1, and B2). Metabolite C was detected only In the high dose groups, indicating that metabolism of CGA-169374 is dose related and involves saturation of the metabolic pathway. Free triazole metabolite was dete6ted in the urine of triazole labeled groups and its byproduct was detected In the liver of phenyl labeled groups only. Other urinary metabolites were not characterized.

A.3 EXECUTIVE SUMMARIES FOR SUPPORTING TOXICITY STUDIES

ORAL TOXICITY

STUDY TYPE: 13 Week Oral Feeding Study – Rat OPPTS 870.3100 MRID 42090022

EXECUTIVE SUMMARY: CGA-169374 Technical was administered orally in feed admixtures to six groups of rats of both sexes at 0 ppm, 20 ppm, 200 ppm, 750 ppm, 1500 ppm, and 3000 ppm for 13 weeks. The results of this dietary subchronic evaluation of the toxicity of the test article were generally unremarkable. There was a significant trend for decreased body weights in both sexes, and the 200 ppm female rats showed an approximate 10% decrease in body weight relative to their controls concomitant with decreased food consumption. There was one dose—related effect of the chemical discovered during the histopathology examination, that identified modest diffuse hepatocellular enlargement, vis a vis. increased liver weights, in rats of both sexes at the two highest doses tested. Additionally, although not statistically significant, compared to the other groups there was an increase in the frequency and quantity of ketones in the urine of group 6 males. The presence of elevated ketone levels may be due to gluconeogenesis driven by decreased protein intake from the diet as a result of decreased food intake. The somewhat compromised nutritional status of the rats could possibly and indirectly have promoted the hepatocellular enlargement as well.
It is possible to conclude from this study, that based on approximately 10% decrease in body weight in the 200 ppm females (concomitant with a negative trend for food consumption) and increases in absolute liver weights in both sexes appearing at 750 ppm, the LOAEL is 200 ppm. The NOAEL was 20 ppm.
Core Classification: Minimum

STUDY TYPE: 26 Week Oral Feeding study –dog OPPTS 870.3150 MRID 42090012

EXECUTIVE SUMMARY: CGA 169374 was offered in feed admixtures to five groups of beagle dogs composed of three animals/group/sex in dietary concentrations of 0 ppm, 100 ppm, 1000 ppm, 3000 ppm, or 6000 ppm for a minimum of 28 weeks. None of the dogs DOS. Compound— related effects, developed essentially at the 3000 ppm and 6000 ppm dose levels. The singularly most striking compound effect was bilateral lenticular cataracts ophthalmoscopically-observed in all dogs at 6000 ppm and in one female beagle at 3000 ppm. Additionally, iridic changes (irregular pupillary margins, miosis), secondary to lens induced uveitis, were also present in the affected animals. There were also reductions in mean body weight in females and males at 6000 ppm test compound throughout the study; weight loss was observed during the first three weeks on study. Body weight loss was precipitated by moderate to severe reductions in mean food consumption in females and males at 6000 ppm during the study with slight reductions observed in males at 3000 ppm and 1000 ppm and in one female at 3000 ppm. Furthermore, there were slight reductions in values for red blood cell count, hemoglobin, and hematocrit in females and males at 6000 ppm. There were also decrements in some serum clinical chemistry measurements including calcium and total protein in females at 6000 ppm and moderate increases in serum alkaline phosphatase in one or both sexes at 3000 ppm. There were modest alterations in several absolute and/or relative organ weight measurements to include the heart, prostate gland, salivary gland, uterus, kidney, liver, and brain at the highest dose tested

(HOT). Nevertheless, liver weight measurements were also increased in Group 4 females. There were no other test article—related changes in any other parameter examined. On the strength of the available data as they relate to the dose levels tested and the parameters observed, **the** LOAEL and the NOAEL for the test article in female and male beagle dogs were 3000 ppm and 1000 ppm, respectively, based primarily on microscopic examination of CGA 169374-related lenticular cataracts. Core Classification: Minimum

STUDY TYPE: 13 Week Oral Feeding Study – mouse OPPTS 870.3100 MRID 42090021

EXECUTIVE SUMMARY: CGA 169374 was offered in feed admixtures to five groups of mice composed of 15 animals/group/sex and 20 mice per sex for controls in dietary concentrations of 20 ppm, 200 ppm, 2500 ppm, 7500 ppm, or 15000 ppm for 13 weeks. Most of the mice fed 7500 ppm or 15,000 ppm test article, groups 5 and 6 respectively, died during the first week on study. There were some CGA 169374-related effects. The statistical analysis of total food consumption and body weight changes over the course of the study showed significantly reduced body weight gain for paired group 4 (2500 ppm) females and a significant negative trend. Compound—related effects from histologic xamination were confined to the liver. Hepatotoxicity in mice that DOS was evidenced by hepatocellular enlargement and necrosis of individual hepatocytes. Those mice that survived to the end of the study showed hepatotoxicity that included hepatocellular enlargement in group 4 animals and group 3 males and hepatocytic vacuolization in group 4 animals. Furthermore, coagulative necrosis was observed in the livers of 4/9 group 4 females. This finding, however, was not considered treatment related, because the foci were frequently small and random. The animals in groups 5 and 6, which represent the unscheduled deaths, had a high incidence of changes consistent with stress. The changes included lymphoid depletion or necrosis of the spleen, lymph nodes, and thymus, hypocellularity of the femoral marrow, mucosal erosion/ulceration of the glandular stomach, and in the female mice necrosis of individual cells in the adrenal cortex, specifically in the zona reticularis. Hyperkeratosis of the nonglandular stomach was observed in males especially from group 6. The study director suggests the "stress" effects may be related to inappetence and a failure to eat as opposed to a direct effect of the test article. On the strength of the available data as they relate to the dose levels tested and to the parameters observed, the body weight changes and the liver histopathology form the basis for setting the NOAEL at 20 ppm, and the LOAEL at 200 ppm. The mortality data indicate the MTD was exceeded and is likely S 7500 ppm.

STUDY TYPE: Subchronic Neurotoxicity OPPTS 870.6200b

EXECUTIVE SUMMARY: In a subchronic neurotoxicity study (MRID 46950329) difenoconazole technical (94.5% w/w, batch no. WM806228) was administered to groups of 12 male and 12 female Alpk:AP$_f$SD (Wistar-derived) rats at concentrations of 0, 40, 250, or 1500 ppm in the diet for 90 days. Respective dose levels corresponded to 0, 2.8, 17.3 or 107.0 mg/kg bw/day for males and 0, 3.2, 19.5, or 120.2 mg/kg bw/day for females. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in 12 animals/sex/group pretest and during weeks 2, 5, 9, and 14. Cholinesterase activity was not determined. At study termination, 5 animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. Of the perfused animals, 5/sex from the control group and 5/sex

from the 1500 ppm group were subjected to histopathological evaluation of brain and peripheral nervous system tissues. Treatment with difenoconazole at concentrations up to 1500 ppm in the diet had no effect on mortality or clinical signs. Relative to respective control weight, final body weight of males and females in the 1500 ppm group was reduced by 9% and 7%. Body weight gain was reduced by 22% in males and 23% in females. Food consumption was reduced in this group (statistically significant only in females [7%]), and food efficiency was significantly reduced in males by 21% ($p \leq 0.05$) and in females by 21% (ns). Lower dose groups were unaffected. Absolute liver weight in males and females in the 1500 ppm group was increased over respective control weight by 38% and 45%. Liver was not weighed in lower dose groups. The increase in liver weight was considered a normal response to chemical treatment.

During weeks 2, 9 and 14, hind-limb grip strength in males in the 1500 ppm group was reduced by 18 to 27% relative to the control values. At week 14, hind-limb grip strength in males in the 250 ppm group was significantly ($p \leq 0.05$) reduced by 20% relative to the control values. FOB observations in females were unaffected by treatment. Motor activity was unaffected in both sexes at all observation times. Brain weight was unaffected by treatment and there were no treatment-related neuropathological lesions.

The LOAEL in male rats is 250 ppm in the diet (17.3 mg/kg bw/day), based on decreased hind limb strength. The NOAEL is 40 ppm (2.8 mg/kg bw/day).

The LOAEL in female rats is 1500 ppm in the diet (120.2 mg/kg bw/day), based on decreased body weight, body weight gain and food efficiency. The NOAEL is 250 ppm (19.5 mg/kg bw/day). The study is classified as **Acceptable/Guideline**

STUDY TYPE: Two-generation reproduction study – rat OPPTS 870.3100 MRID 42090018

EXECUTIVE SUMMARY: EXECUTIVE SUMMARY: In a two generation reproduction study, difenoconazole was administered in the diet to male and female rats at 0, 25, 250, or 2500 ppm [0, 1.25, 12.5, or 125 mg/kg/day, respectively]. Statistically significant reductions in body weight gains of F0 and F1 males were observed at 2500 ppm during Days 70-77 and during the course of the study [terminal body weight minus Day 0 body weight]. Significant reductions in body weight gains of F0 and F1 females were seen during the pre-mating, gestation, and lactation periods. A dose-related, but non-statistically significant decreases in body weight gain was seen in F0 females at 250 ppm during Days 70-77 prior to mating, Days 0-7 of gestation, and Days 7-14 of lactation:
At 2500 ppm, significant reductions in pup body weight were detected on Days 0, 4 [pre- and post culling], 7, 14, and 21 for males and females of both generations. There was a significant reduction in the body weight of F1 male pups on Day 21 in the 250 ppm group. The percentage of male pups in the F1 generation surviving Days 0-4 was significantly reduced in the 2500 ppm group:
For parental toxicity, the LOAEL of 250 ppm [12.5 mg'kg/day is based on the decreased maternal body weight gain; the NOAEL is 25 ppm [1.25 mg/kg/day. For offspring toxicity, the LOAEL of 250 ppm [12.5 mg/kg/day] is based on decreased pup weights at Day 21; the NOAEL is 25 ppm [1.25 mg/kg/day].

STUDY TYPE: Developmental toxicity-rabbit OPPTS 870.3700b MRID 42090017

EXCUTIVE SUMMARY: CGA 169347 technical was administered by gavage on days 7—19 ofgestation to p;esumed pregnant rabbits at 0, 1, 25, or 73 mg/kg. Maternal toxicity was observed in this study as the death of one doe and abortions observed in two other high dose does. In addition, significant reductions in body weight gain of high dose does, were present days 7-10, 10—14, 7-20, and 0—29. These reductions correspond with reduced feed consumption during these intervals (significant reductions in feed consumption in the HDT were only observed during the treatment period, not after treatment). Slight nonsignificant increases in postimplantation loss and resor?tions/doe were observed in the HOT. The significant decrease in fetal weight at the HDT may have been due to treatment. The significant differences in fetal weight observed at the low and mid dose were apparently not due to treatment.
Core Classification: supplementary
Maternal NOAEL = 25 mg/kg; Maternal LOEL = 75 mg/kg
Developmental Toxicity NOAEL 25 mg/kg; Developmental Toxicity LOEL = 75 mg/kg

STUDY TYPE: Developmental toxicity-rat OPPTS 870.3700a MRID No.: 42090016

EXECUTIVE SUMMARY: CGA 169347 technical was administered by gavage on days 6-15 of gestation to presumed pregnant rats at 0, 2, 20, 100, or 20a mg/kg. Significant decreases in maternal body weight gain and feed consumption were observed during the dosing period for thefeed consumption were observed during the dosing period for the 100 and 200 mg/kg groups. These animals also exhibited a significant increase in the incidence of excess salivation. There was a non significant decrease in the mean number of fetuses per dam, and non significant increases in the mean number of resorptions per dam and % postimplantation loss in the 200 mg/kg group. There was a slight (non significant) decrease in mean fetal body weight at the 200 mg/kg group. The following represents the significant alterations in the development of fetuses in the 200 mg/kg group. The incidence of bifid or unilateral ossification of the thoracic vertebrae was significantly increased on the fetal basis. There were also significant increases in the average number of ossified hyoid and decreases in the average number of sternal centers of ossification (per fetus per litter). The average number of ribs was significantly increased (with accompanying increases in the number of thoracic vertebrae), and decreases in the number of lumbar vertebrae in this group. These findings may be related to maternal toxicity. This study may be upgraded after satisfactory review of the response to the noted deficiencies.
core classification: supplementary
NOTE: Due to the relatively high percent deviation of the actual doses tested from the theoretical concentration the effect levels have been modified accordingly. This modification may be subject to change as the purity is currently unknown.
Maternal NOAEL = 16 mg/kg; Maternal LOEL = 85 mg/kg
Developmental Toxicity NOAEL = 85 mg/kg; Developmental Toxicity LOAEL = 171 mg/kg

STUDY TYPE: Acute Neurotoxicity - Rats OPPTS 870.6200a [81-8]; OECD 424.

EXECUTIVE SUMMARY: In an acute neurotoxicity study (MRID 46950327), groups of

fasted Alpk:APfSD Wistar-derived rats (10/sex/dose), at least 42 days old, were gven a single oral dose of difenoconazole technical (CGA169374) (94.3% w/w, batch/lot # WM806228) in 1% w/v aqueous carboxymethylcellulose (CMC) at doses of 0, 25, 200, or 2000 mg/kg bw and observed for 14 days. Dose levels selected for this study were based on the results of preliminary acute neurotoxicity study (MRID 46950325). Neurobehavioral assessmçnt (ifinctional observational battery and motor activity testing) was performed on 10 animals/sex/group on days -7, 1, 8, and 15. Body weight and food consumption were measured weekly throughout the study. At study termination, 5 animals/sex/group were euthanized and perifised in situ for neuropathological examination; brain weight was recorded from these animals. Of the perfused animals, 5 animals/sex from the control and high dose groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

There were no unscheduled deaths at any dose level. Weight change on the day of dosing by the control, low-, mid-, and high-dose groups was -2.1, - 1.0, -7.8, and -18.3 g, respectively, for males and 0.0, 2.1, -3.8, and -13.0 g, respectively, for females. Body weight for females had recovered to control levels by day 8. Food consumption for males given 2000 mg/kg was approximately 20% less than control during week 1 only ($p<0.01$). Food consumption for these animals recovered to control levels during week 2. There were no differences from control for females at any dose level or for males at the lower dose levels. These effects on body weight and food consumption were not toxicologically significant.

At 2000 mg/kg, a number of adverse clinical signs were observed on day I (at the time of **peak** effect), including: upward curvature of the spine (8 males, 9 females); tip-toe gait (3, 8); decreased activity (6, 7); piloerection (3, 5); sides pinched in (3, 7); and subdued (1, 0). Females were affected more than males. All treatment-related clinical signs observed on day 1 showed complete recovery by day 5 (males) or day 7 (females).
Significant decreases in fore-limb grip strength were seen in mid- (23%) and high-dose (26%) males on day 1. Females dosed with 2000 mg/kg had lower motor activities on day 1 (37%), at the time of peak effect, and on day 8 (31%). Males dosed with 200 or 2000 mg/kg had higher motor activities than the controls on day 1, 50% and 55%, respectively, at the time of peak effect. There were no effects on brain weight at any dose level. Neuropathological examination of the central and peripheral nervous system showed no effects of treatment at doses of 2000 mg/kg in both sexes.
The LOAEL for acute neurotoxicity of difenoconazole technical (CGA169374) in male rats is 200 mglkg bw based on reduced fore-limb grip strength in males on day 1. The NOAEL is 25 mg/kg bw. The LOAEL for acute neurotoxicity of difenoconazole technical (CGA169374) in female rats is 2000 mg/kg. Based on decreased body weight, the following clinical signs: upward curvature of the spine, tip-toe gait, decreased activity, piloerection and sides pinched in, and decreased motor activity. The NOAEL is 200 mg/kg bw.

STUDY TYPE: Chronic Toxicity in Dogs OPPTS 870.4100b MRID 42090012

EXCUTIVE SUMMARY: CGA 169347 was administered in the diet to male and female dogs at 0, 20, 100, 500, or 1500 ppm. The NOAEL was 100 ppm and the LOAEL was 500 ppm based on the following. Females receiving 1500 ppm in the diet had a significant reduction in body weight gain on day 7. Females in the 500 and 1500 ppm groups, although not

statistically significant, had inhibited body weight gain throughout the study. These animals also had significant reductions in food consumption on days 7, 35, 70, and 357. The reduction in mean percent reticulocytes at the highest dose tested on day 359 may have been related to treatment, Significant increases (treatment related at day 85; dose—related at days 175 and 359) were observed in alkaline phosphatase in males receiving 1500 ppm. This study may be upgraded upon satisfactory review of the registrants response to the deficiencies (submission of the purity and raw daily observation data).
Classification: core—supplementary

STUDY TYPE: Combined Chronic Toxicity/Carcinogenicity Study in Rats
OPPTS 870.4300 MRIDs 42090019/ -20

EXECUTIVE SUMMARY: CGA 169374 was administered in the diet to male and female rats [80/sex/dose] for 104 weeks at 0; 10; 20; 500; and 2500 ppm. There were reductions in cumulative body weight gains in the 500 and the 2500 ppm gi'oups. Mean liver weight was inëreased at week 53 and t termination in the 2500 ppm group . Hepatocellular hypertrophy was observed in the 500 and the 2500 ppm animals at termination. Additional findings in the clinical chemistry data also indicated that liver was the primary target organ for toxicity. No treatment related increased incidences of neoplastic findings were observed in this study. The NOAEL for the study was 20 ppm which was equal to 0.96 and 127 mgikgid for males and females respectively. The LOAEL was 500 ppm equal to 24.12 and 32.79mg/kg/day for males and females respectively based on cumulative decreases in body weight gains. Discussion of Tumor Data No treatment related increased incidences of neoplastic findings were observed in this study. Adequacy of the Dose Levels Tested The dose levels tested were considered adequate by the Cancer Peer Review Committee. (memorandum of July 27,1994 from B. Rinde of the Health Effects Division)

STUDY TYPE: Carcinogenicity Study in Mice OPPTS 870.4200b MRIDs 42090015 and 42710006

EXECUTIVE SUMMARY: CD-I mice were feddiets containing difenoconazole at 0; 10; 30; 300; 2500or 4500 [males only] for 78 weeks. The NOAEL was 30 ppm equal to 4.65 mgfkg/d in males and 5.63mg/kg/d in females respectively. The LOAEL was 300 ppm equal to 46.29 mg/kg/cL in males and 57.79mg/kg/d in females based on reductions in the cumulative body weight gains at the higher dose levels.
Discussion of Tumor Data: Difenoconazole was reviewed by the HED-CPRC on May 18,1994 (memorandum of July 27, 1994 from E. Rinde of the NED CPRC to C. Giles-Parker of RD) and classified as a Category C carcinogen with out a q-star. The margin-of-exposure [MOEI approachL was selected because there was only very weak (limited) evidence of carcinogenic potential at dose levels not considered to be excessive with significant changes observed only at excessive doses. There was no evidence for genotoxicity. There was a statistically significant increase in liver adenomas, carcinomas, and combined liver adenomas and carcinomas in both sexes at doses of 2500 and 4500 ppm. These doses were considered to be excessively high for cancer testing. Liver necrosis and liver adenomas were also noted in males at 300 ppm. There were no statistically significant increases in liver tumors at 10 or 30 ppm. Adequacy of the Dose Levels Tested: The Health Effects Division Cancer Peer Review Committee considered the doses

adequate and the study acceptable.

DERMAL TOXICITY

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

December 18, 2008

MEMORANDUM

SUBJECT: **Difenoconazole - with both available in vivo and in vitro dermal absorption studies, select an appropriate dermal absorption factor to be used for risk assessment.**

PC Code: 128847 **DB Bar Code:** NA

FROM: Jonathan Chen, Ph.D., Senior Toxicologist Jonathan Chen 12/18/08
Jenny Tao, M.D. Senior Toxicologist 12/18/08
Risk Assessment and Science Support Branch (RASSB)
Antimicrobial Division (7510P)

TO: Marshall Swindell
Product Manager, Team #33
Regulatory Management Branch I / AD

THROUGH: Norman Cook, Branch Chief 12/18/08
RSSB/AD (7510P)

Synonym: 1-{2-{4-(4-Chlorophenoxy)-2-chlorophenyl}-4-methyl-1,3-dioxolan-2-ylmethyl}-1H-1,2,4-triazole, CGA169374

Formulation: **Difeno-Shield™**

Active Ingredient:

Difenoconazole .....32.8% a..i.

The technical ingredient has a purity of >99% a.i.

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Applicant: Syngenta Crop Protection, Inc., Greensboro, N.C. 37419

Use: Difeno-Shield is fungistatic agent that controls and/or inhibits the growth of many fungi associated with odor, staining and discoloration. Difeno-Shield can be applied to paper, wallboard, paint, coatings, caulks, sealants, adhesives, textiles and plastic. It provides an invisible barrier to inhibit the fungal organisms associated with mold and mildew that cause odor staining and discoloration. Difeno-Shield is not intended to protect users or others against food-borne or disease causing organisms. Difeno-Shield is not for use in food or feed handling areas.

Background and Conclusion:

On October 9, 2008, there is AD Toxicity Endpoint Selection Committee special working group meeting held been held to address the appropriate way to use the *in vitro* study results. Attached is the meeting minute.

There are four Difenoconazole dermal absorption studies.
In vivo Dermal Penetration in the Rat, MRID: 47453201
In vivo Dermal Penetration in the Rat, MRID: 46950333
In vitro Absorption through Human Epidermis; MRID: 47453202
In vitro Absorption through Rat Epidermis; MRID: 47453203

The working group considers both available in vivo and in vitro dermal absorption studies, and an estimated Dermal Absorption factor of 6.0 % was decided to be used in future risk assessment.

Special Working group Meeting
AD Toxicity Endpoint Selection Committee
Potomac Yard, Room S-8621

Meeting Minutes
October 9, 2008

Attendees

Stephen Dapson ..... HED
Pv Shah ..... RD
John Redden ..... RD
Jonathan Chen ..... AD
Jenny Tao ..... AD
Michelle Centra ..... AD

This special working group of the AD Toxicity Endpoint Selection Committee (ADTC) is organized to discuss following Issues:

- The current Office of Pesticide (OPP)'s position in handling the information generated with in vitro dermal absorption studies.
- Using difenoconazole as an example, with both available in vivo and in vitro dermal absorption studies, select an appropriate dermal absorption factor to be used for risk assessment.

Jonathan Chen chaired this meeting.

Issue One: The current Office of Pesticide (OPP)'s position in handling the information generated with in vitro dermal absorption studies.

Jonathan Chen points out in creosote RED risk assessment Agency already used an approach of comparing the in vitro studies (Rat skin vs. human skin), calculated an adjustment factor, and applied to the dermal absorption factor selected from in vivo study. Both Pv Shah and Steve Dapson indicate North American Free Trade Agreement (NAFTA) did prepare a draft dermal absorption group position paper on using the in vitro dermal absorption data in risk assessment . In the draft documents, major points are listed below:

1. use of in vitro data as the sole basis for derivation of a Dermal Absorption Factor (DAF) for human health risk assessment is not recommended;
2. Under the situation when both in vitro studies (human and animal) studies and an in vivo animal study are available, the vitro data may be used to extrapolate to human equivalent DAFs for risk assessment.
3. Under this approach, if an in vitro technique performed using animal skin is shown to be a good predictor of animal in vivo dermal absorption for a particular compound, then the same technique conducted in vitro with human skin may be useful in extrapolating to humans. The relationship can be demonstrated as following formula.

IF	$\frac{\text{Animal } \textit{in vitro}}{\text{Animal } \textit{in vivo}} \approx 1$	THEN	Human *in vitro* ≈ Human DAF

Working Group Conclusion:

- Although the NAFTA's position paper is not finalized yet, PV indicated both Health Canada's Pest Management Regulatory Agency (PMRA) and HED management approved this approach. AD should consider it is an appropriate approach in using the in vitro study information;
- The approach should be evaluated on a case-by-case base; and
- In the case when the data set consisting of a "Triple Pack" of in vitro human and animal studies and an in vivo animal study conducted using identical test material can be used to extrapolate human DAF for risk assessment, using following formula

Estimated Human DAF = Adjustment Factor x Animal in vivo DAF

Where

$$\textbf{Adjustment Factor} = \frac{\textbf{Human in vitro DAF}}{\textbf{Animal in vitro DAF}}$$

Note: After the meeting, Steve Dapson sends the most recent NFTA's Draft to the group (See Attachment 1).

Issue Two: Using difenoconazole as an example, with both available in vivo and in vitro dermal absorption studies, select an appropriate dermal absorption factor to be used for risk assessment.

For difenoconazole, there are four dermal absorption studies.

In vivo Dermal Penetration in the Rat, MRID: 47453201
In vivo Dermal Penetration in the Rat, MRID: 46950333
In vitro Absorption through Human Epidermis; MRID: 47453202
In vitro Absorption through Rat Epidermis; MRID: 47453203

Four Different Steps are taken in determine the proposed DAF

Step 1. Determine the appropriate dermal absorption factor based on *in vivo* dermal absorption studies.

There are two *in vivo* dermal absorption studies. The executive summary of these two studies are listed below.

***In vivo* Study 1:**
Roberts, K. and Jones, B. (2007). Difenoconazole technical in vivo dermal penetration study in the rat. Central Toxicology Laboratory, Cheshire, UK. Report Number UR0908-REG, February 6, 2007. MRID 47453201. Unpublished.

In the dermal penetration study (MRID 47453201), Difenoconazole (99.1% a.i.) and [^{14}C] Difenoconazole (>98% a.i. radiochemical purity, Batch reference: AMS 255/4) was applied to the skin (10 cm^2) of male Han Wistar rats (16 rats/dose).

Sample doses were prepared by the Sponsor (0.5% carboxy-methylcellulose (CMC) used as vehicle) and applied at a rate of 10 $\mu L/cm^2$ as an aqueous dilution of the concentrate 1/100 (1 mg a.i./mL) or 1/10 (10 mg a.i./mL), aqueous dilutions of the concentrate or as a concentrate (100 mg a.i./mL), corresponding to applied nominal doses of 10, 100, or 1000 $\mu g/cm^2$, respectively.

Exposure duration was 10 hours after application and animals were monitored up to 72 hours post-dosing. Subgroups of rats (4/dose) were terminated at 10, 24, 48, and 72 hours post-dosing. Skin washings, application site materials, excreta, selected tissues, blood and animal carcasses were analyzed for radioactivity.

The majority of the applied doses (80-92%) remained on the skin surface and was readily removed with mild washing indicating that aqueous solutions of [^{14}C]-difenoconazole are poorly absorbed through rat skin. Absorption of [^{14}C]-difenoconazole, though minimal, generally, increased over time for all applied dose concentrations.

Mean Combined Absorption values of [^{14}C]-difenoconazole from the 0.1% (1 mg/ml/10 ug/cm^2) dose was 11.3%, 13.8%, and 13.0% at 10, 24, and 72 hours, respectively. Mean Combined Absorption values of [^{14}C]-difenoconazole from the 1% (10 mg/ml/100 ug/cm^2) dose was 4.1%, 4.3%, and 5.3% at 10, 24, and 72 hours, respectively. Mean Combined Absorption values of [^{14}C]-difenoconazole from the 10% (100 mg/ml, concentrate/1000 ug/cm^2) dose was 1.4%, 2.4%, and 2.8% at 10, 24, and 72 hours, respectively.

For this study, the working group decides a dermal absorption factor of 13.8% (0.1% , 24 hours after exposure) should be the appropriate dermal absorption factor.

***In vivo* Study 2:**
Hassler, S. (2003). Difenoconazole 250 EC (A7402G): Dermal absorption of [Triazole-U-14C] CGA 169374 formulated as Score® 250 EC (A-7402G) in the rat (in vivo). Syngenta Crop Protection AG, CH-4002 Basel, Switzerland. Report Number 051AM-1, May 6, 2003. MRID 46950333. Unpublished.

In the *in vivo* dermal penetration study (MRID 46950333), [Triazole-U-^{14}C] CGA 169374 formulated as SCORE® 250 EC (Batch No. ILA 50.2-1, ILA 50.2-2 (radiolabeled, >98%a.i.)

and AMS 255/3 (non-radiolabeled, >98%a.i.) was applied to the skin (10 μL/cm^2) of 4 male HanBrl: WIST (SPF) rats/dose/treatment at three dose levels: 0.5 (P1), 13 (P2), 2.5μg/cm^2 (P3 and P3a). The results of the high dose level (Group P3) showed a high variability in the efficiency of the washing procedure which did not allow for reliable evaluation of dermal absorption; therefore the high-dose dermal application was repeated and assigned as Group P3a. The nominal exposure duration was 6 hours, at which time the dermal absorption of the test substance was determined. The amount remaining in/on the skin at the application site after washing was determined at three additional time points 24, 48, or 72 hours after application in order to estimate the depletion of the dose. Urine, feces, and blood were collected. The applied concentrations of the low and medium dosages were intended to approximate realistic concentrations recommended for use in the field, whereas the high dose was undiluted product.

Recoveries of the applied doses were 95-104%. The **Total Mean Combined Absorbed Dose (%)** over a specific time period was calculated as exposed skin site (skin strips and remaining treated skin) plus excreta (urine, feces, and cage wash), carcass (all organs), and blood had conflicting results across the doses. After the 6 hour exposure 27, 13, and 9% of the dose was totally absorbed (skin, whole blood, g.i. tract, remaining carcass, feces urine) in the low, mid-, and high-dose group, respectively. At 24 hours, after exposure 6 hour of low, mid- and high dose groups would be 48, 19 and 8 % of the total absorbed dose.

However there was a high level of variation between individual animals in the same dose group. The low and mid-dosed animals show an increase in absorbed dose from 6 to 24 hours and a slight decrease at 48 and 72 hours. However, the high-dose group did not show an increase from 6 until 48 hours with a substantial decrease in radioactivity at 72 hours. The majority of the absorbed radioactivity was isolated in the gastrointestinal tract or carcass at 6 and 24 hour, with increasing amounts found in the feces at 48 and 72 hours. Blood residues during and after dermal exposure at all doses were mostly at or below the limit of detection, the highest blood residues levels were reached between 6 and 8 hours after administration, accounting for 0.01 ppm and 0.25 ppm CGA 168374 equivalents for the middle and high dose levels, respectively. The majority of the radioactivity was washed off and the rinsate was analyzed as CGA 169374 equivalents.

For this study, the working group decides a dermal absorption factor of 48 % (0.5 μg/cm^2, 24 hours after exposure) should be the appropriate dermal absorption factor.

In conclusion, the working group decides a dermal absorption factor of 48 % should be the appropriate dermal absorption factor based on the *in vivo* dermal absorption studies (MRIDs 47453201 and 46950333).

Step 2. Determine the appropriateness of the in *in vitro* dermal absorption studies.

There are two *in vitro* dermal absorption studies: *in vitro* Absorption through human epidermis (MRID: 47453202) and *in vitro* absorption through rat epidermis (MRID: 47453203). Working group concluded that in the calculation of the dermal absorption, the percent dermal absorption should include the chemical concentration absorbed in the epidermis and amount in receptor fluid. The two studies are summarized below.

***In vitro* Study 1:**

Gledhill, A. (2007). Difenoconazole technical: In vitro absorption through rat epidermis final report. Report Number JV1923-REG0R2, June 28, 2007. MRID 47453203. Unpublished.

In a dermal penetration study (MRID 47453203) Difenoconazole (99.1% a.i.) and [^{14}C] Difenoconazole (>98% a.i. radiochemical purity, Batch reference: AMS 255/4) was applied to the epidermal membranes of male rats of the Wistar Crl: (WI)BR strain at a rate of 10 µL/cm2 as preparations representing an 10, 100, or 1000 µg/cm2. Exposure duration was 10 or 24 hour periods, during which receptor fluid was sampled at specific time intervals. Any difenoconazole remaining on the skin after the two exposure periods was removed by washing.

For the 10-hour exposure period, the percent dermal absorbed are 26%, 2.8% and 2.9 % of the applied dose of 10, 100, or 1000 µg/cm2, respectively. For the 24-hour exposure period, the percent dermal absorbed are 40%, 17% and 3.3 % of the applied dose of 10, 100, or 1000 µg/cm2, respectively. The Study Results for the 24-hours post application is summarized in Table 1.

Table 1 Summarize the Difenoconazole in each matrix at 24 hours post-application from in vitro Rat dermal absorption study (Gledhill, 2007, MRID 47453203)

Matrix analyzed	Amount of difenoconazole in each matrix 24 hours post-application		
	Percent of Applied Does (mean ± SEM)		
	1000 µg/cm^2 (n=5)	100 µg/cm^2 (n=6)	10 µg/cm^2 (n=5)
Donor chamber	0.21 ± 0.19	0.40 ± 0.30	0.29 ± 0.14
Skin wash	98.7 ± 1.58	73.9 ± 3.97	52.8 ± 3.35
Epidermis	2.37 ± 0.67	14.8 ± 2.01	2.51 ± 0.51
Amount in receptor fluid	0.91 ± 0.25	3.67 ± 0.63	37.1 ± 2.55
Total Recovery	102 ± 1.52	93.1 ± 5.82	92.7 ± 1.13
Percent dermal Absorption [1]	3.3%	17%	40%

Note: 1. Percent Dermal Absorption = the total Amount of difenoconazole in epidermis and amount in receptor fluid.

In vitro Study 2:

Davies, D. (2007). *In Vitro* absorption through human epidermis final report. Central Toxicology Laboratory, Cheshire,UK. Report Number JV1922-REG-R1, January 26, 2007. MRID 47453202. Unpublished.

In a dermal absorption study (MRID 47453202), Difenoconazole (99.1% a.i.) and [14C] Difenoconazole (>98% a.i. radiochemical purity, Batch reference: AMS 255/4), was administered to human epidermal membranes at a rate of 10 µL/cm2 as preparations representing a 10, 100, or 1000 µg/cm2. Exposure duration was 10 or 24 hour periods, during which receptor fluid was sampled at specific time intervals. Any difenoconazole remaining on the skin after the two exposure periods was removed by washing.

The applications in this study were designed to simulate potential human dermal exposure arising from the normal use of this type of formulation. The distribution of difenoconazole absorption in the skin was determined for 10 and 24 hours, and a 24 hour absorption profile (µg/cm2/h) was determined. At 10 hours, absorption was 3.46%, 1.15%, and 0.44% for 10, 100, and 1000 µg/cm2, respectively. At 24 hours, the absorption was 4.54%, 1.30%, and 0.40% for the 10, 100, and 1000 µg/cm2, respectively. The Study Results for the 24-hours post application is summarized in Table 2.

Table 2. Summary of the Difenoconazole in Each Matrix at 24 hours Post-application from *in vitro* Human Dermal Absorption study (Davis, 2007).

Matrix analyzed	Amount of difenoconazole in each matrix 24 hours post-application		
	Residues in matrix (Mean % of applied dose) [1]		
	1000 µg/cm^2	100 µg/cm^2	10 µg/cm^2
Donor chamber	0.02	0.14	0 .17
Skin wash	96.4	81.6	102
Stratum corneum	0.16	0.52	0.50
Remaining epidermis	0.15	0.35	0.70
Amount in receptor fluid	0.09	0.43	3.34
Total Recovery (sum of above)	96.8	83.0	107
Percent dermal Absorption [2]	0.40 %	1.30%	4.54%

Note: 1. Mean of 6 samples/group.
2. Percent Dermal Absorption = The total Amount of difenoconazole in Stratum corneum, remaining epidermis and Amount in receptor fluid.

In the discussion, following limitations in the both of the two *in vitro* studies are identified.

1. After the skin sample is carefully removed from the site, the skin was soaked in 1.5 M sodium bromide for 20 minutes and rinsed after soaking with distilled water, and the epidermis was peeled from the dermis. Working group suggested that it would have better to dermatomed the skin (350-450 micron) rather than chemical separating , should be included in the dermal absorption study; and

2. The epidermis is stored frozen in aluminum foil until it is needed. Although the membrane integrity was determined by measurement of the electrical resistance across the skin membrane: membranes with a measured resistance, working group still consider freezing of the skin sample is not recommended.

However, because limitations of the dermal absorption studies are similar between the *in vitro* rat dermal absorption and the *in vitro* human dermal absorption study, and the *in vitro* rat DAF is equivalent to the rat in vivo DAF. Therefore, working group concluded that the in vitro dermal absorption studies are appropriate to be used to establish DAFs for risk assessment.

Step 3. Identify the appropriate Adjustment Factor for extrapolating from Rat DAF to Human DAF.

Working group decides the 24-hour exposure period is more appropriate in comparing the difference between in vitro rat *vs.* human skin studies. Table 1 summarizes the difenoconazole in each matrix at 24 hours post-application from in vitro rat dermal absorption study (Gledhill, 2007, MRID 47453203). Table 3 summarizes the calculated ratio of in vitro human dermal absorption factor vs. in vitro rat dermal absorption of difenoconazole .

Table 3. Summarize the Calculated Ratio of *in vitro* Human Dermal Absorption Factor (DAF) vs. *in vitro* Rat Dermal Absorption Factor of Difenoconazole .

Calculated DAF	Percent dermal Absorption		
	1000 µg/cm^2	100 µg/cm^2	10 µg/cm^2
In vitro Human DAF [1]	0.40 %	1.30 %	4.54 %
In vitro Animal DAF [2]	3.3 %	17 %	40 %
Ratio	0.12	0.07	0.11

Note: 1. Derived from the summary of the Rat dermal absorption study (Gledhill, 2007, MRID 47453203), Table 1.
2. Derived from the summary of Human Dermal Absorption study ((Davis, 2007, MRID 47453202), Table 2.

Step 4. Calculation of the Estimated Dermal Absorption Factor

The Working group decides data set give the highest ratio should be used as the adjustment factor. Therefore, the dataset derived from 1000 $\mu g/cm^2$ which gave the highest ratio of 0.12 should be used for the derivation of the estimated human dermal absorption factor.

Therefore, based on the formula

Estimated Human DAF = Adjustment Factor x Animal in vivo DAF

$$= 0.12 \times 48\% = 5.76\% \text{ (Ca. 6\%)}$$

Therefore, a human estimated DAF of ca. 6 % should be used for risk assessment.

Working Group Conclusion:

Considering both available *in vivo* and *in vitro* dermal absorption studies, an estimated Dermal Absorption factor of 6.0 % should be used in future risk assessment.

B. REVIEW OF HUMAN RESEARCH

Klonne, D. (1999) Integrated Report for Evaluation of Potential Exposures to Homeowners and Professional Lawn Care Operators Mixing, Loading, and Applying Granular and Liquid Pesticides to Residential Lawns: Lab Project Number: OMA005: OMA001: OMA002. Unpublished study prepared by Riceerca, Inc., and Morse Laboratories. 2213 p. (MRID 44972201).

The PHED Task Force, 1995. The Pesticide Handlers Exposure Database, Version 1.1. Task Force members Health Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association, released February, 1995.

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